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PhD. Thesis

Development of Synthetic Methods for Fluorinated Compounds Using Organoboron Compounds

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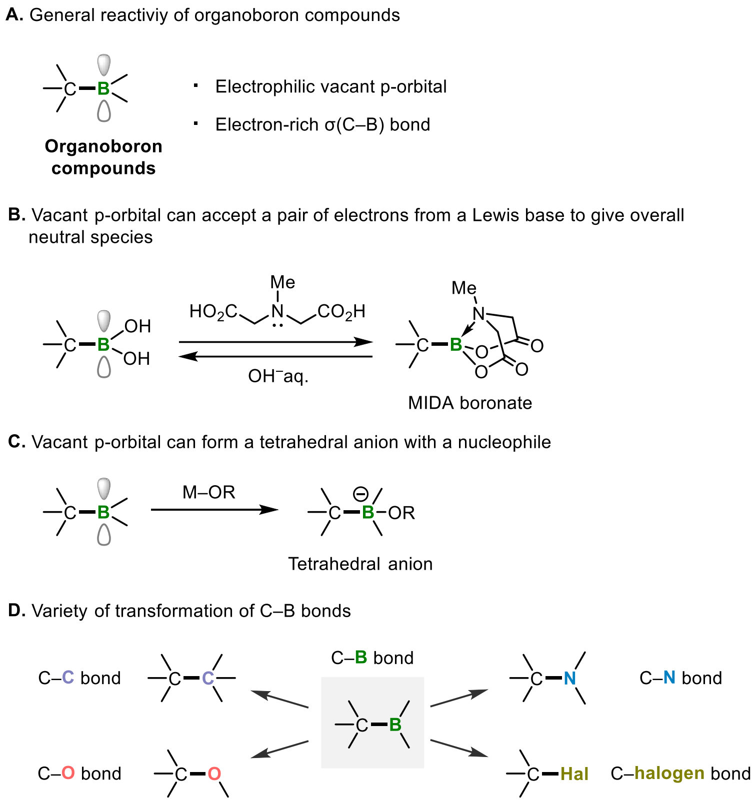
Contents

I General Introduction

1.1 Organoboron compounds

Organoboron compounds are a general term for functionalized organic compounds that have a bond between the boron atom and the carbon atom.[1] Organoboron compounds show nucleophilic and electrophilic reactivity, which depends on reaction conditions and substituents on the boron atom, because of the mixing nature of the slightly polarized and electron-rich nature of the C–B bond and Lewis acidity at the boron center (Figure 1A). Furthermore, organoboron compounds in their three-coordinate form have a vacant p-orbital and can form a boronate complex by accepting a pair of electrons from a Lewis base to give overall neutral species (e.g., MIDA boronate) or form a tetrahedral anion with a nucleophile (Figure 1B, C).[1,2] Moreover, organoboron compounds are different from other organometal compounds, such as organolithium and organozinc compounds, in terms of stability under the air and moisture. Since their character and stability, organoboron have been applied to a variety of transformations as valuable synthetic intermediates in organic synthesis. For instance, the boron moiety is oxidized and applied for stereospecific carbon–carbon and carbon–heteroatom bond-forming reactions (Figure 1D).[3,4]



A. General reactiviy of organoboron compounds

B. Vacant p-orbital can accept a pair of electrons from a Lewis base to give overall neutral species

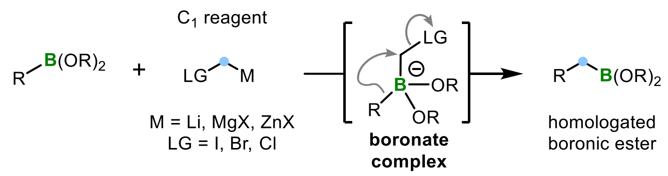
C. Vacant p-orbital can form a tetrahedral anion with a nucleophile

D. Variety of transformation of C–B bonds

Figure 1. The nature of the organoboron compounds and their reactivity

Since certain organoboron compounds are stable, the process to activate organoboron compounds is sometimes needed in organic reactions. Organoboron compounds form ate-complexes, what we call boronate complex, when nucleophiles such as organolithium reagent or alkoxide coordinate to the vacant p-orbital of the boron atom. The activated organoboron compounds sometimes show unique reactivity and improve the reaction efficiency. For instance, boronate complexes activated by organolithium reagents induce a stereospecific 1,2-metallate rearrangement and afford single carbon homologated products via Matteson homologation (Figure 2A).[5] It is considered that the "ate complex" activated by alkoxide may involve the transmetalation step in Suzuki-Miyaura borylation reaction to improve the reaction efficiency (Figure 2B).[6] Since their initial application in organic synthesis several decades ago, the continued development of organoboron chemistry has increased exponentially.

A. Matteson homologation



B. Catalytic cycle of Suzuki-Miyaura borylation reaction

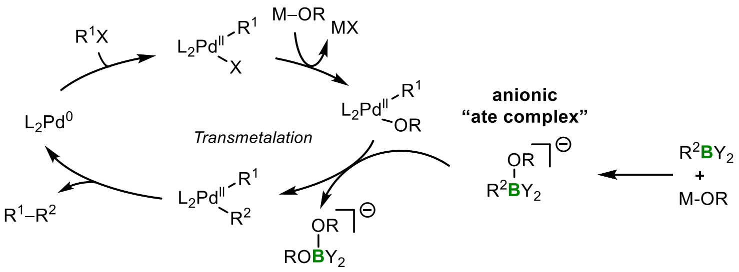
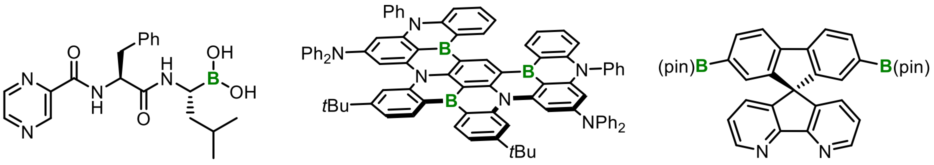


Figure 2. Examples of activation of organoboron compounds in reaction

Moreover, recently, organoboron compounds have been used as synthetic intermediates and boron-containing pharmaceuticals, organic materials, and catalysts (Figure 3).[7-9] Bortezomib, which is known as one of the anticancer drugs, has boron moiety to inhibit the proteasome reversibly. ω-DABNA, multiple-resonance thermally activated delayed fluorescence emitters, is synthesized by Hatakeyama group via a sequential multiple borylation reaction. Otherwise, remote steric control for undirected meta-selective C–H borylation of arenes was developed by Ilies group in 2022. In this research, a new ligand was developed for borylation reaction. New synthetic methods of organoboron compounds to construct these new entries of organoboron compounds are required to develop these compounds.



Pharmaceuticals
(Bortezomib, anticancer drug)

Material science
(ω-DABNA, OLED material)

Organic synthesis
(C-H borylation ligand)

Figure 3. Pharmaceutical and material applications of organoboron compounds

1.2 Borylation reactions

The first borylation reaction, which is a non-catalytic procedure was reported by the Frankland group in 1860. They synthesized an organoboron compound via nucleophilic substitution on an electrophilic boronic ester with an organozinc reagent (Figure 4).[10] Later, as the famous and practical non-catalytic borylation reaction, the hydroboration reaction was developed by the Brown group in 1956 (Figure 4).[11]

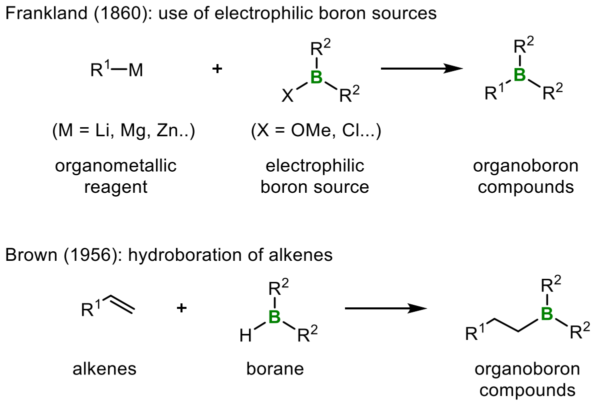


Figure 4. Non-catalytic borylation reaction

The hydroboration of alkenes usually gives the organoboron compounds in an *anti*-Markovnikov manner. On the other hand, the catalytic borylation reaction also has been investigated for preparing the organoboron compounds. Nöth group reported the first catalytic hydroboration of unactivated aromatic alkenes by use of rhodium(I) catalysis with catechol borane as the boron source in 1985 (Figure 5).[12] This reaction affords the corresponding terminal alkyl boronates in an *anti*-Markovnikov manner.[13] Among the other well-known borylation reactions, Miyaura–Ishiyama borylation and Hartwig-Miyaura C–H borylation are known as powerful methods to construct C(aryl)–B bond or C(sp^3)–B bond. The group of Miyaura and Ishiyama reported borylation of aryl halides by use of a palladium(II) catalysis and diboron reagent as the boron source in 1995 (Figure 5).[14, 15] On the other hand, the Hartwig group developed borylation of C(sp^3)–H bonds by use of boryl-manganese, -rhenium and -iron complexes in 1995.[16, 17] And then, they developed the catalytic version of the C(sp^3)–H bond borylation reaction using iridium- and rhodium catalysts in 2000 (Figure 5).[18] In 2002, the Ishiyama and Hartwig group developed the C(aryl)–H bond borylation using Iridium catalysis (Figure 5).[19] Following these seminal works, many types of catalytic borylation reactions have been developed until now.

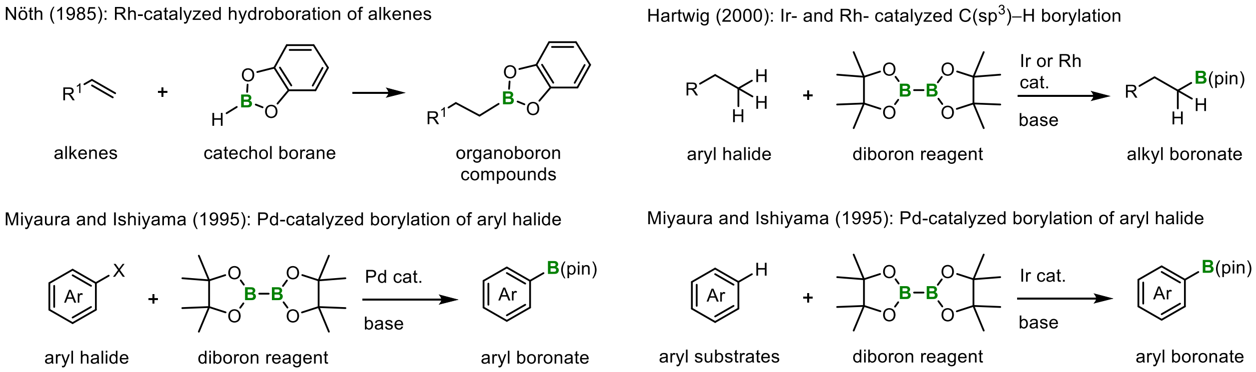
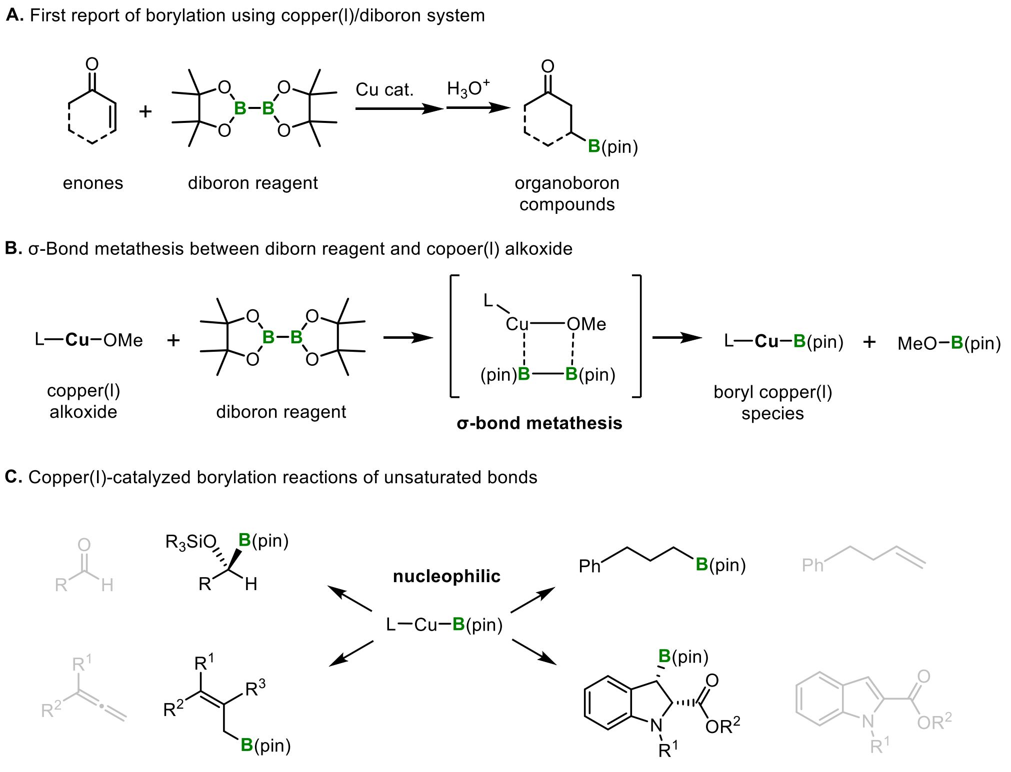


Figure 5. Catalytic borylation reaction

1.3 Copper(I) /diboron system for borylation reactions

In 2000, the Hosomi and Ito group and the Miyaura and Ishiyama group independently developed copper(I)-catalyzed borylation reaction of enone substrates as a Michael acceptor using a diboron reagent, bis(pinacolate) diboron as the boron source (Figure 6A).[20-23] The nucleophilic active catalyst species, boryl copper(I) intermediate, is generated in situ via σ-bond metathesis between the diboron reagent and a copper(I) alkoxide (Figure 6B).[24-26] The boryl copper(I) species coordinates and inserts to enone substrates, then furnishes the alkyl copper(I) intermediate. Finally, the subsequent protonation gives the corresponding protoboration product. Following this pioneer works, a variety of electrophiles has been applied to the borylation reactions, e.g., conjugated esters, allylic electrophile, carbonyl compounds, and imines to date (Figure 6C).[26] In 2000 and 2001, the Miyaura and Ishiyama group developed the borylation of unactivated multiple bonds with the use of boryl copper(I) species via the boryl cupration of the multiple bonds. (Figure 6C).[27, 28] Afterward, these types of borylation reactions of the other unsaturated bonds, e.g., alkenes, allenes, dienes, and enynes, have been developed (Figure 6C).

The copper(I)/diboron system can also be applied to the boryl substitution of aryl and alkyl halides.[29-31] In 2009, the first Miyaura borylation of aryl halides using copper(I)/diboron system was developed by Lin and Marder group.[32] Also, Steel, Marder, and Liu group and the Ito group independently reported the boryl substitution reaction of alkyl halides in 2012.[33, 34] And then, an enantioconvergent borylation reaction of secondary alkyl halides was developed by the Ito group.[35]


A. First report of borylation using copper(I)/diboron system

B. σ-Bond metathesis between diborn reagent and copoer(I) alkoxide

C. Copper(I)-catalyzed borylation reactions of unsaturated bonds

Figure 6. Various borylation reactions with copper(I)/diboron system

1.4 Organofluorine compounds

Fluorine atom(s) plays an important role in both medicinal chemistry and material chemistry when introduced into molecules, as it can change their biological and physical properties (Figure 7).[36, 37] For example, the fluorine atom(s) can improve the metabolic stability and membrane permeability of medicines.[38] In 2022, there were 19 novel small-molecule drugs approved by the FDA. Among the approvals, there are four drugs containing fluorine atom(s).

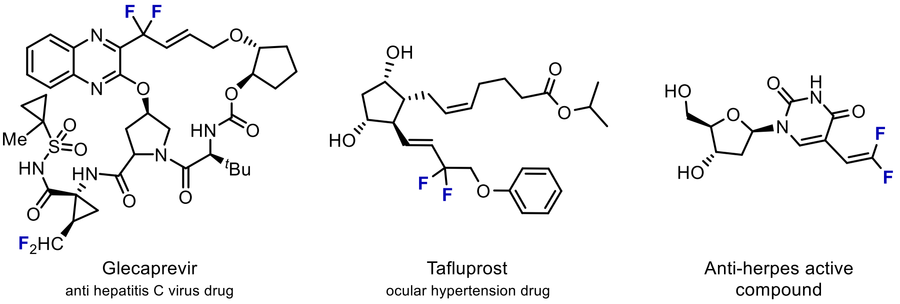


Figure 7. Examples of fluorine-containing drugs and bioactive compound

Moreover, the chemical structures containing fluorine atom(s) are considered as versatile bioisosteres, e.g., functional mimetic of the hydrogen atom, the methyl group, ether, and amide moieties because of their electronic properties and relatively small atomic radius (Figure 8).[39]

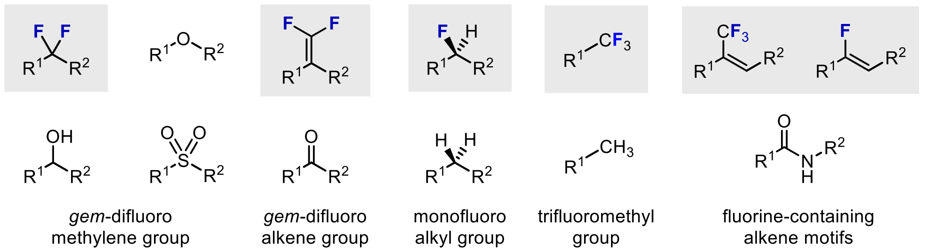


Figure 8. Fluorinated motifs can be used as bioisostere of several functional groups

These unique physical and biological character of fluorine moieties have attracted much attention by many scientists over the years. In 1926, synthesis of the first organofluorine compound, carbon tetrafluoride (CF_4) was achieved. [40] In the early research of fluorination reaction, HF and F_2 gas were often used as fluorination reagents. However, a special reactor and techniques are needed to use these reagents because of their high reactivity and their corrosive features. The Schiemann group developed a chemical reaction in which a primary aromatic amine is converted into an aryl fluoride via a diazonium tetrafluoroborate intermediate in 1927 (Figure 9).[41] This reaction is a valuable reaction in terms of the fact that it does not use a gaseous fluorination reagent. However, this reaction needed a high temperature to proceed the reaction. Following these backgrounds, numerous of synthetic methods to construct organofluorine compounds, including monofluorination, trifluoromethylation, and others under mild conditions have been developed until now.[42–46]

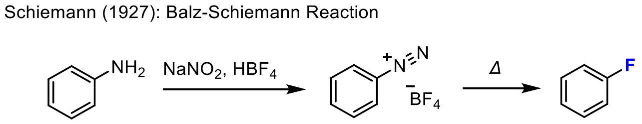
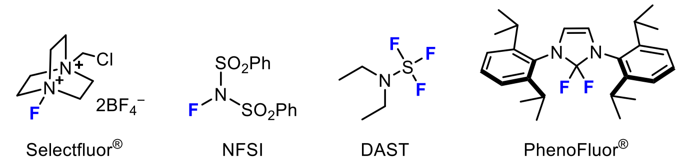
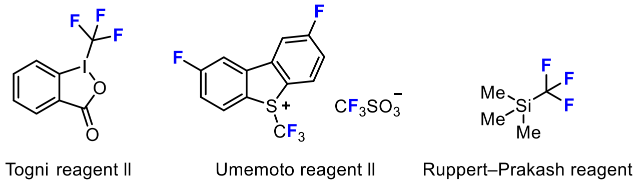


Figure 9. Balz-Schiemann reaction

Recently, the development of fluorination reagents was accelerated. The fluorination reagents are mainly divided into two types of reagents. One is the electrophilic fluorination reagents, in which the electron-deficient fluorine atom acts as the reaction active species. Another one is nucleophilic reagents, in which fluorine anion acts as the reaction active species. For example, there are electrophilic fluorination reagents such as Selectfluor® and NFSI and nucleophilic fluorination reagents, e.g., DAST and PhenoFluor® (Figure 10A).[44,47,48] Trifluoromethylation reagents are also investigated; for example, there are electrophilic trifluoromethylation reagents such as Togni reagent II and Umemoto reagent II and nucleophilic trifluoromethylation reagent such as Ruppert-Prakash reagent (Figure 10B).[49,50] Although there is a variety of methods to introduce the fluorine atom(s), it is still challenging to construct highly functionalized organofluorine compounds because of the highly reactive fluorination reagent. Moreover, the fluorination reagents sometimes require harsh reaction conditions. Following these backgrounds, the development of new methods for the synthesis of highly functionalized organofluorine compounds under mild conditions is still highly desired.



A. Monofluorination reagents



B. Trifluoromethylation reagents

Figure 10. Examples of electrophilic and nucleophilic fluorination reagents

1.5 Overview of this thesis

In this thesis, I focus on developing new methodologies for novel organofluorine compounds and shows the utility of these compounds by the transformation toward the valuable organofluorine compound.

Chapter 2 describes the copper(I)-catalyzed enantioselective γ-boryl substitution of trifluoromethyl- and silyl-substituted alkenes via β-fluoro-elimination (Figure 11). Several substrates, which substituted a variety of silyl groups were reacted with bis(pinacolato)diboron in the presence of a copper(I) salt and an optically active C_1 symmetric QuinoxP*-type bisphosphine ligand. The products in this reaction, which are silyl-substituted *gem*-difluoroallylboronates were obtained in good yield with high enantioselectivity. Furthermore, the products would be useful fluorinated optically active building blocks because derivatization of the boron moiety and silicon moiety, as well as allylboration, would construct highly functionalized and *gem*-fluorinated structural motifs, which have never been synthesized before, including quaternary stereogenic carbon centers.

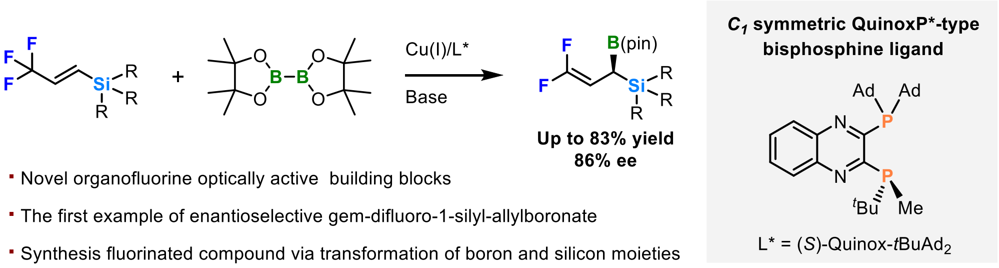


Figure 11. Graphical abstract of Chapter 2

Chapter 3 describes the synthesis of fluoromethylated cyclopropanes, which contains a variety of substituents, through the electrophilic cyclization via the boronate complex between various homoallylic boronates and Selectfluor® (Figure 12). This reaction provides fluoromethylated cyclopropane rings that were difficult to synthesize by previous methods. The key to the success of this reaction is phenyl lithium reagent, which activates the homoallylic boronate and affords the boronate complex. The presence of boronate complex in this reaction was confirmed by ^{11}B NMR experiments. I also applied the synthesis of a building block, including fluoromethyl-substituted cyclopropane, for a bioactive compound use of the product.

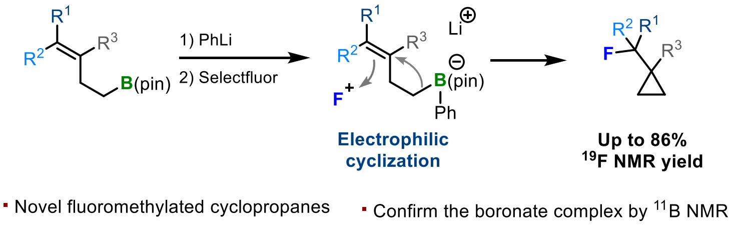


Figure 12. Graphical abstract of Chapter 3

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II Cu(I)-Catalyzed Enantioselective γ-Boryl Substitution of Trifluoromethyl- and Silyl-substituted Alkenes

2.1. Introduction

As described in the general introduction, the new effective methods for the functionalized organofluorine compounds and fluorine-containing molecules are still highly desired. Following these demands, the fluorine-containing organoboron compounds have been recognized as a useful building block and have attracted much attention recently because of access to the functionalized organofluorine compounds via the transformation of boron moiety (Figure 1).

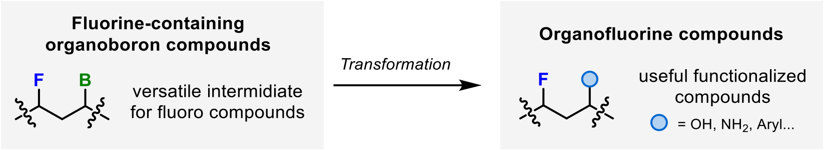


Figure 1. The utility of fluorine-containing organoboron compounds

In 1989, the first report for the synthesis of fluorine-containing organoboron compounds was developed by Ichikawa group.[1] They used the β-CF_3 *p*-toluenesulfonate as a substrate and generated β,β-gem-difluoro-α-tosyloxyvinylanion by the reaction with a stoichiometric amount of LDA. This vinyl anion reacted with alkyl boranes via 1,2-migration of the alkyl group from the boron atom on the vinylic carbon to afford the β,β-gem-difluoroalkenylborane in situ. The β,β-gem-difluoroalkenylborane can be transformed into a variety of fluorinated compounds subsequently (Figure 2). For example, the protonolysis of β,β-gem-difluoroalkenylborane undergo by the treatment with acetic acid. Moreover, oxidation of the boron moiety by adding an aqueous solution of H_2O_2 afforded the corresponding difluoromethyl ketones. Iodination also could be applied to the use of I_2 and provided difluorinated iodo compounds. 1,1-Difluoro-1-alkenes was obtained by the reaction with bromine and NaOMe via 1,2-migration of β-alkyl group.

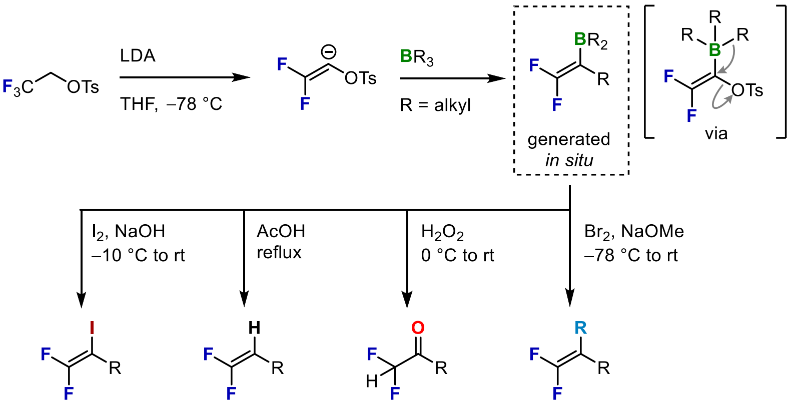


Figure 2 First report for the synthesis of fluorine-containing organoboron compounds and their transformations

The first study for the catalytic synthesis of fluorine-containing organoboron compounds with transition metal was reported by Brown in 1999 (Figure 3).[2] The reason why much research to construct fluorine-containing organoboron compounds using catalytic amount of transition metal catalysts were developed over the year.[3]

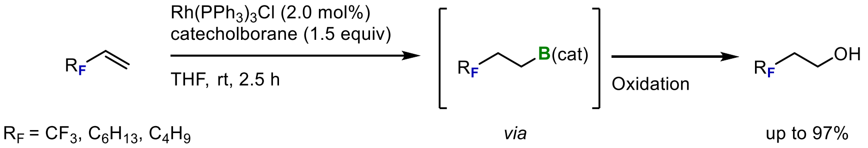


Figure 3. The first example of catalytic synthesis of fluorine-containing organoboron compound use of transition metal catalysis

Focused on the reactions use of copper catalysis, the Hoveyda group reported the first synthesis of difluoroallylboronates use of boryl-copper(I) species in 2011. The key to the success of this reaction is β-fluoro elimination (Figure 4).[4]

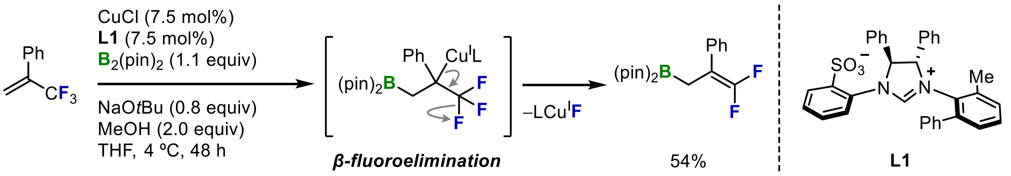


Figure 4. The first example of copper(I)-catalyzed boryl-substitution of trifluoromethyl substituted alkene

The synthesis of enantioenriched *gem*-difluoroallylboronates use of copper(I) catalysis was reported from Ito, Shi, and Hoveyda groups independently (Figure 5).[5-7] Ito and Shi groups have used the similar (*R*,*S*)-Josiphos type ligand **L2** and **L3** to obtain the desired difluoroallylboronates with high enantioselectivity. On the other hand, the Hoveyda group has used the chiral NHC ligand **L4**. In these reactions, substituents on alkene moiety are the alkyl group or aryl group.

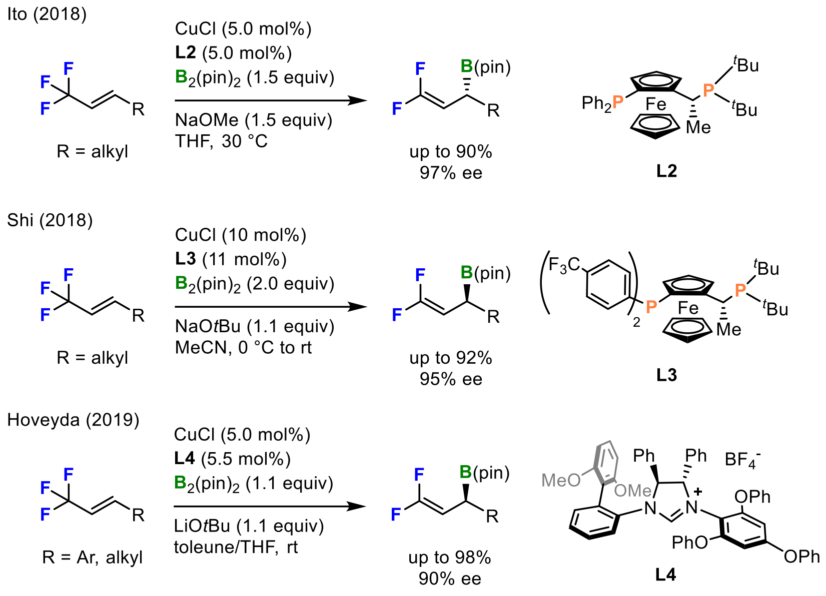


Figure 5. Enantioselective boryl-substitution of trifluoromethyl substituted alkenes

Silicon atom is located in group 14 main elements in the periodic table and shows a similar character to carbon atom. Moreover, silicon atom forms σ bond with carbon atoms to form a variety of organosilicon compounds. On the other hand, silicon atom is different from carbon atom in terms of atomic radius, electronegativity, and atomic orbital since silicon atom belongs to the third period in the periodic table. Thus, organosilicon compounds sometimes show the characteristic reactivity not found in carbon compounds.[8] In addition, the organosilicon compounds have been used as a versatile intermediate and organoboron compounds because of their stability under the air and water, e.g., Hiyama cross-coupling and Tamao oxidation.[9,10]

Otherwise, the organic molecule containing boron and silicon moiety can be applied to the stepwise transformation. Since the boron moiety is more reactive than the silyl moiety, the boron moiety was transformed into another functional group; then the silyl moiety was converted into another functional group. For example, the Hiyama group demonstrated a stepwise transformation of boron and silyl moiety (Figure 6).[11]

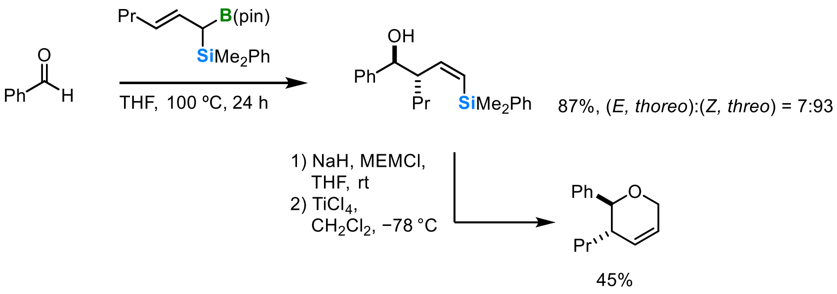


Figure 6. Stepwise transformation of boron and silyl moiety

The silicon-containing organic molecules have also been attracted as pharmaceuticals and functional organic materials for bioimaging and molecular sensors (Figure 7). The silicon atom is sometimes used as a mimic of the carbon atoms in pharmaceuticals.[12] Furthermore, the silicon atom enhances the electronic or physical property of organic molecular because of the unique orbital overlap of silicon atom.[13]

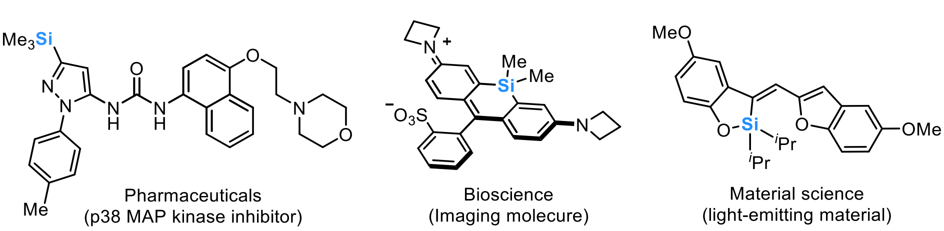


Figure 7. Application of organosilicon compounds

As I described in the section of fluorine-containing organoboron compounds, fluorine-containing organosilicon compounds also have attracted attention as versatile fluorinated-building blocks for the preparation of novel fluorine compound because of the transformability of organosilicon compounds. Organosilicon compounds containing a β,β-*gem*-difluoroalkene moiety are recognized as a useful building. The first report of synthesis of racemic *gem*-difluoroallylsilanes was developed by Feng in 1997 (Figure 8).[14] After this seminal work, several methods have been developed to synthesize racemic *gem*-difluoroallylsilanes by Crimmin, Shi, Ogoshi and Feng around 2010's.[15-20]

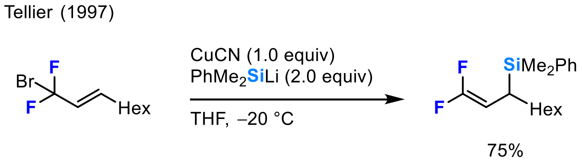


Figure 8. Seminal work of synthesis of racemic *gem*-difluoroallylsilanes

The synthesis of enantioenriched γ,γ-gem-difluoroallylsilane was achieved by using copper(I) catalysis in Shi and Hoveyda group independently (Figure 9). Both groups have used the chiral NHC ligands **L5** and **L6** to obtain the desired difluoroallylsilanes with high enantioselectivity.[21,22]

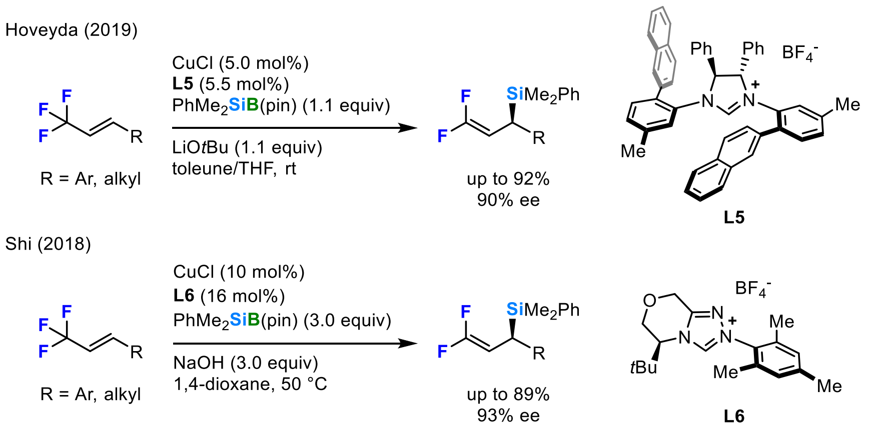
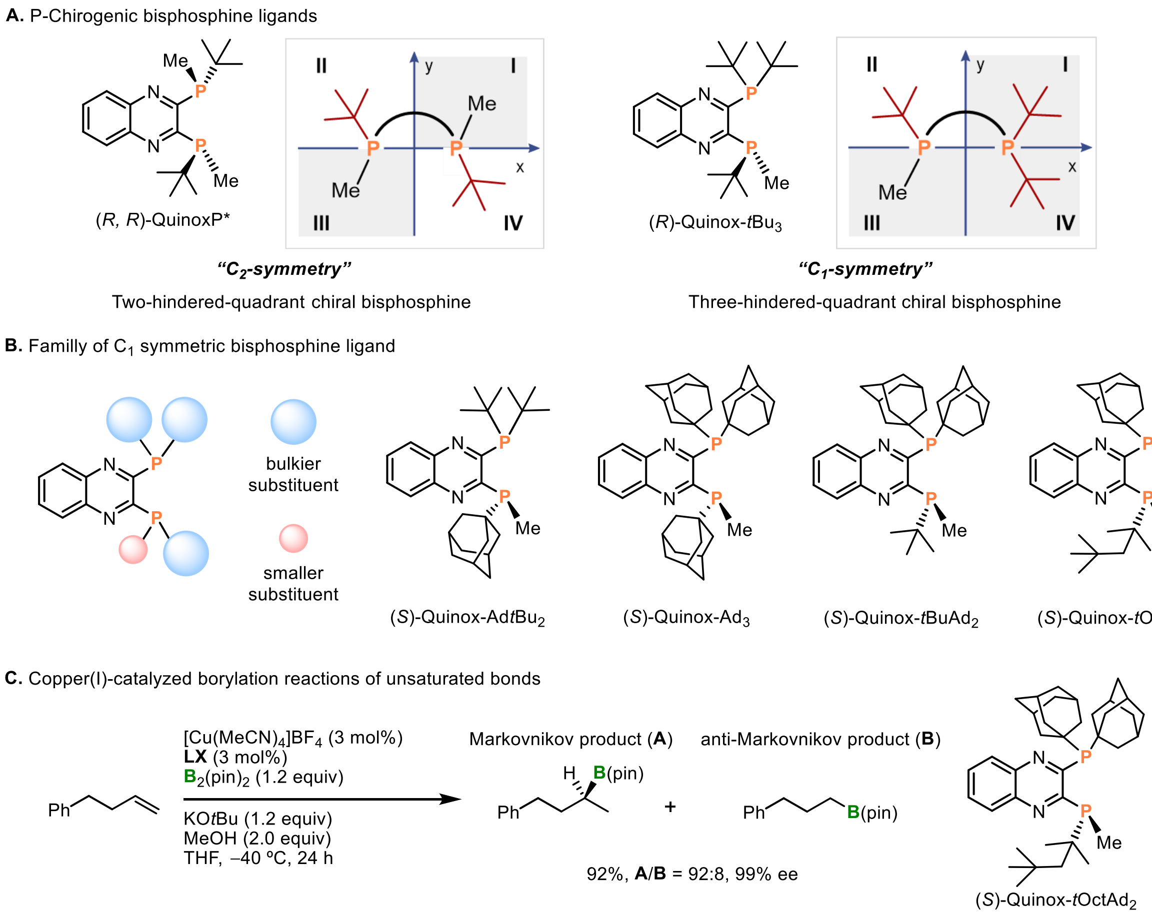


Figure 9. Enantioselective silyl-substitution of trifluoromethyl substituted alkenes

In 2005, Imamoto and Yoshida group developed QuinoxP* as a new C_2 symmetric bisphosphine ligand (Figure 10A).[23] This ligand can be prepared in one-pot from commercially available 2,3-dichloroquinoxaline and a chiral phosphine anion. This ligand has a stereocenter on phosphorus atoms and quinoxaline backbone, which has a strong electron-withdrawing ability that decreases the electron density at the phosphorus atoms. This ligand exhibits excellent enantioselectivities in both Rh-catalyzed asymmetric hydrogenations and Rh- or Pd-catalyzed carbon–carbon bond-forming reactions compared to most of the previously reported phosphine ligands, which has a stereocenter on phosphorus atom. Later, the Imamoto group developed (*R*)-Quinox-*t*Bu$_3$ as new three-hindered quadrant phosphine ligands (Figure 10A).[24] These C_1 symmetrical ligands show good to excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of selected dehydroamino acid derivatives, enamides, and ethenephosphonates. Based on these great works, novel three-hindered-quadrant P-chirogenic bisphosphine ligands containing bulkier substituents on the phosphorus atoms were developed by Ito's group in 2018 (Figure 10B).[25] The best ligand, (*S*)-Quinox-*t*OctAd$_2$ showed high enantioselectivity in copper(I)-catalyzed Markovnikov hydroboration (Figure 10C).



A. P-Chirogenic bisphosphine ligands

B. Familly of C_1 symmetric bisphosphine ligand

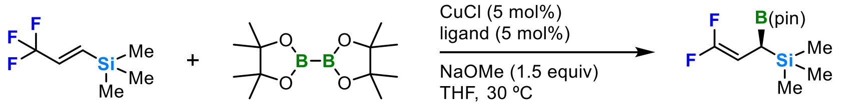
C. Copper(I)-catalyzed borylation reactions of unsaturated bonds

Figure 10. Modification of QuinoxP*-type ligands and their application

2.2. Results and discussion

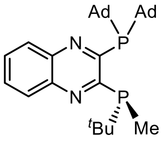
The development of a copper(I)-catalyzed enantioselective borylation reaction is described in Table 1. The reaction was started with (*E*)-trimethyl(3,3,3-trifluoro-1-propenyl)silane (**1a)** and bis(pinacolato)diboron (**2**) (2.0 equiv) in the presence of CuCl (5 mol%), (*S*)-Quinox-*t*BuAd$_2$ (5 mol%), and NaOMe (1.5 equiv) in THF at 0 to 30 °C afforded the *gem*-difluoro allylicboronate (*S*)-**3a** in good yield with high enantioselectivity (83% ^{19}F NMR yield, 86% ee (entry 1)).[25,26] On the other hand, (*S*)-Quinox-Ad$_3$ as other C$_1$ symmetric QuinoxP*-type bisphosphine ligand, in which the *t*Bu group on the chiral phosphorus atom in (*S*)-Quinox-*t*BuAd$_2$ was replaced by a bulkier adamantyl group, gave (*S*)-3a with slightly decreased enantioselectivity (70% ^{19}F NMR yield, 84% ee, entry 2).[25] Moreover, (*S*)-Quinox-Ad*t*Bu$_2$, which is a less bulky ligand furnished allylicboronate (*S*)-**3a** with lower enantioselectivity when compared to (*S*)-Quinox-*t*BuAd$_2$ (70% ^{19}F NMR yield, 74% ee, entry 3).[25] Other C$_2$ symmetric QuinoxP*-type bisphosphine ligands such as (*R,R*)-BenzP*, (*R,R*)-QuinoxP*, and (*R,R*)-TMS-QuinoxP* were also tested, but these ligands gave (*S*)-**3a** with lower enantioselectivity (entries 4–6, 31–96% ^{19}F NMR yield, –76– –48% ee).[27] Other C$_2$ symmetric bisphosphine ligands such as (*S,S*)-Ph-BPE and (*R*)-DTBM-Segphos were also tested. These ligands gave the desired product (*S*)-**3a** in excellent yield; however, only low to moderate enantioselectivities were observed (entries 7 and 8, 93 and 96% ^{19}F NMR yield, –76 and 8% ee). Finally, I conducted the reaction with (*R,S*)-Josiphos, the best ligand in Ito's group previous study.[5] However, (*R,S*)-Josiphos led to a significant decrease in enantioselectivity (entry 9, 96% ^{19}F NMR yield, –18% ee).

Table 1. Optimization of the reaction conditions.[a]

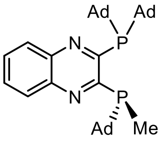


1a **2** (1.5 equiv) (*S*)-**3a**
NMR yield (isolated yield)

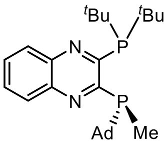
Entry	Ligand	Time (h)	NMR yield (%)[b] (isolated)	% ee
1	(*S*)-Quinox-*t*BuAd$_2$	27	83(77)	84[c,d]
2	(*S*)-Quinox-Ad$_3$	6	70(43)	84[c]
3	(*S*)-Quinox-Ad*t*Bu$_2$	5	70(34)	74[c]
4	(*R*,*R*)-BenzP*	2	93(68)	–76
5	(*R*,*R*)-QuinoxP*	2	31(23)	–72
6	(*R*,*R*)-TMS-QuinoxP*	2	96(73)	–48
7	(*S*,*S*)-Ph-BPE	2	93(73)	8
8	(*R*)-DTBM-Segphos	2	96(66)	–76
9	(R,*S*)-Josiphos	2	96(68)	–18



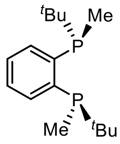
(*S*)-Quinox-*t*BuAd$_2$



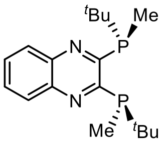
(*S*)-Quinox-Ad$_3$



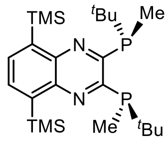
(*S*)-Quinox-Ad*t*Bu$_2$



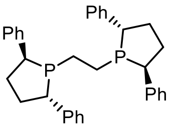
(*R*,*R*)-BenzP*



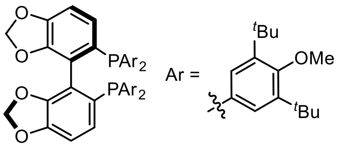
(*R*,*R*)-QuinoxP*



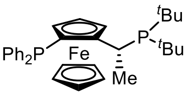
(*R*,*R*)-TMS-QuinoxP*



(*S*,*S*)-Ph-BPE



(*R*)-DTBM-Segphos

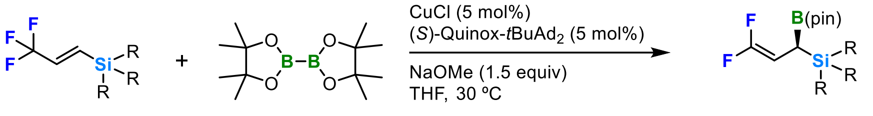


(*R*,*S*)-Josiphos

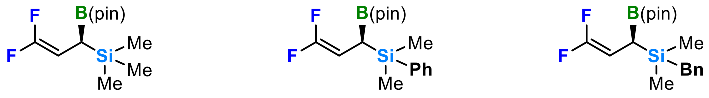
[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.38 mmol), CuCl, chiral ligand (0.013 mmol), and base (0.375 mmol) in THF (0.5 M). [b] Determined using ^{19}F NMR analysis of the crude product with fluorobenzene used as an internal standard. Isolated yields are shown in the parentheses. Determined using high-performance liquid chromatography (HPLC) analysis after oxidation and acylation. [c] Determined using HPLC after allylboration. [d] **1a** was added at 0 °C and the reaction mixture was heated to 30 °C.

Following the results shown in Table 1, I tried to improve the enantioselectivity further using substrates bearing a bulkier substituent on the silicon atom (Table 2). Unfortunately, both substrates bearing a dimethylphenyl silyl group (**1b**) and dimethylbenzyl silyl group (**1c**) gave their corresponding allylboronate products [(*S*)-**3b** and (*S*)-**3c**] with slightly lower ee values (84 and 82% ee, respectively) when compared to that of the allylboronate product bearing a trimethylsilyl group [(*S*)-**3a**].

Table 2. The effect of the silyl group.[a]



1 **2** (1.5 equiv) (*S*)-**3** NMR yield (isolated yield)



(*S*)-**3a**[b] (27 h)
77%, 86% ee

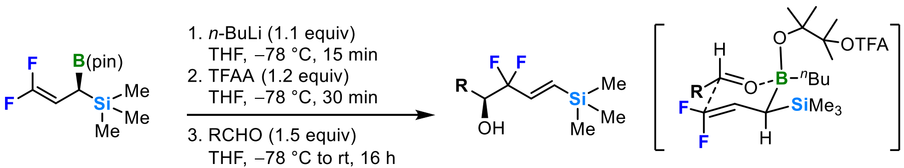
(*S*)-**3b** (8 h)
80%, 84% ee

(*S*)-**3c** (20 h)
74%, 82% ee

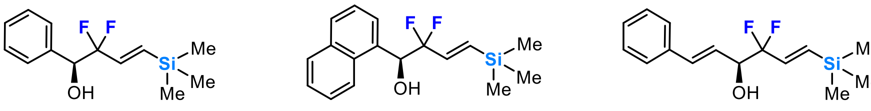
[a] The reaction was performed on a 0.25 mmol scale. The ee values were determined using HPLC analysis after allylboration. Isolated yields are shown. [b] **1a** was added at 0 °C and the reaction mixture was heated to 30 °C.

I then used this method to investigate the utility of synthesizing a variety of fluorinated compounds with more complex structures (Table 3). The stereoselective allylboration of different kinds of aldehydes with (*S*)-**3a** was conducted using the Aggarwal method.[28] I obtained their corresponding homoallylic alcohols in high yield with perfect diastereoselectivity and high stereospecificity (up to 95% yield, E/Z = >99:1, 100% es, Table 3). Benzaldehyde, naphthaldehyde, and cinnamaldehyde were applicable to the allylation reaction (**4a**–**4c**, 71–88% yield, E/Z = >99:1, 84–86% ee, 98–100% es). Furthermore, aromatic aldehydes bearing electron-donating or electron-withdrawing substituents on the aryl group were also acceptable to this reaction and gave the corresponding allylboration product efficiently with excellent stereospecificity (**4d** and **4e**, 82 and 95% yield, E/Z = >99:1, 82 and 86% ee, 95 and 100% es, respectively).

Table 3. Scope of the allylboration reaction using (*S*)-**3a**.[a]



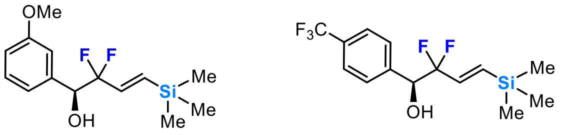
(*S*)-**3a**, 86% ee (*S*)-**4** TS



(*S*)-**4a**
71%, *E/Z* =>99:1, 86% ee

(*S*)-**4b**
81%, *E/Z* =>99:1, 84% ee

(*S*)-**4c**[b]
88%, *E/Z* =>99:1, 86% ee



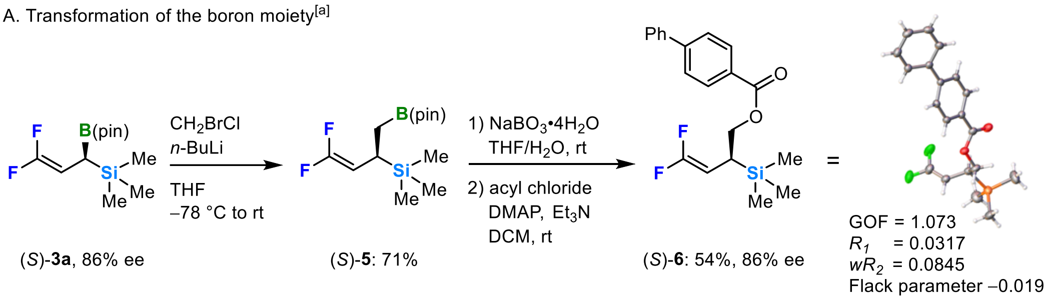
(*S*)-**4d**
82%, *E/Z* =>99:1, 82% ee

(*S*)-**4e**
95%, *E/Z* =>99:1, 86% ee

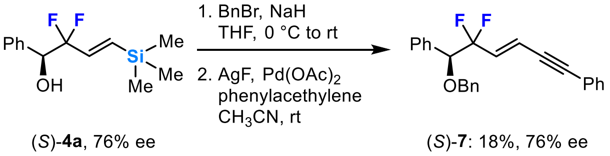
[a] The reaction was performed on a 0.07 mmol scale. The ee values were determined using HPLC analysis. Isolated yields are shown. [b] The reaction was carried out using 1.2 equiv of aldehyde.

The silyl-substituted *gem*-difluoroalkenes synthesized using the copper(I)-catalyzed reaction were applied in a variety of transformations subsequently (Figure 1). Fluorinated allylboronate [(*S*)-**3a**] was applied to a homologation reaction using a halomethyl lithium reagent to furnish the desired product [(*S*)-**5**] in good yield (71%).[29] Subsequent oxidation of the boron moiety and acylation were conducted to afford the acylated product [(*S*)-**6**] in moderate yield (54%) without any erosion of the enantiomeric purity (86% ee, 100% es, Figure 1A). Single-crystal X-ray diffraction analysis of compound **6** was conducted to confirm the structure of the allylboronate product [(*S*)-**3a**]. The newly formed stereogenic carbon centers in **6** have an *S*-configuration. I also conducted an oxidative Sonogashira cross-coupling reaction of (*S*)-**4a** (Figure 1B).[30,31] This reaction affords the optically active 1,3-enynes bearing a *gem*-difluoromethylene moiety without a drop of the enantiomeric purity [(*S*)-**7**] (25% ^{19}F NMR yield, 18% isolated yield, 76% ee, 100% es).

A. Transformation of the boron moiety[a]



B.Transformation of the silyl moiety via oxidative Sonogashira cross-coupling of (*S*)-**4a**[b]



[a] The homologation reaction was performed on a 0.14 mmol scale. The oxidation and acylation reactions were performed on a 0.068 mmol scale. The ee value was determined using HPLC analysis. [b] The benzyl protection reaction was performed on a 0.512 mmol scale. The cross-coupling reaction was conducted on a 0.21 mmol scale. The ee value was determined using HPLC analysis.

Figure 1. Transformations of the allylboronate product.

The author has proposed the plausible catalytic cycle for the enantioselective borylation of trifluoromethyl- and silyl-substituted alkenes, which is described in Figure 2. First, a copper(I) methoxide intermediate **I**, bearing the bisphosphine ligand, is formed in situ and then reacts with diboron reagent to form borylcopper(I) intermediate **II**. Alkene **1a** coordinates to boryl copper(I) intermediate **II** to form complex **III**. The regioselectivity and enantioselectivity are determined in the transition state formed between the coordination and insertion steps, in which the electron-withdrawing CF$_3$ group stabilizes the Cu–C bond. Next, the borylcupration step affords intermediate **IV**.[5] The *gem*-difluoro allylboronate product (*S*)-**3a** was obtained via a β-fluoroelimination step. Finally, the copper(I) complex **V** reacts with a stoichiometric amount of NaOMe to regenerate the copper(I) alkoxide complex **I** and close the catalytic cycle.

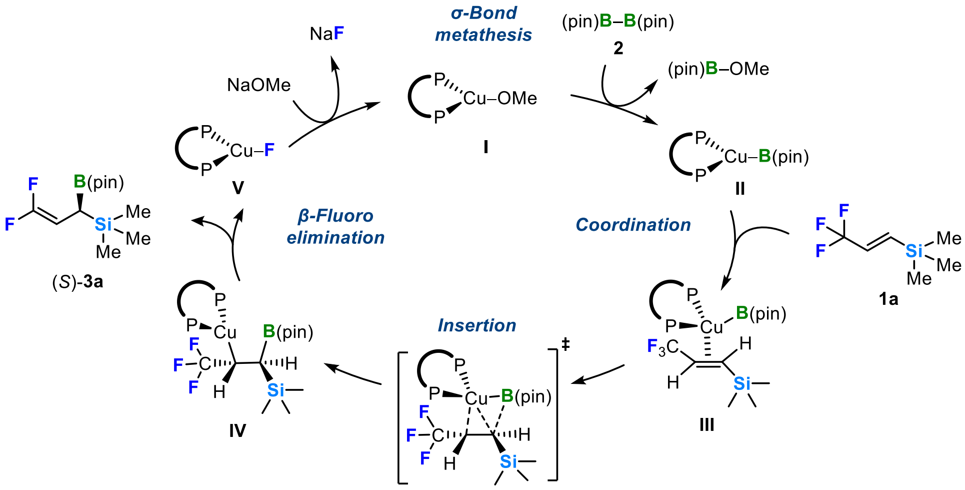
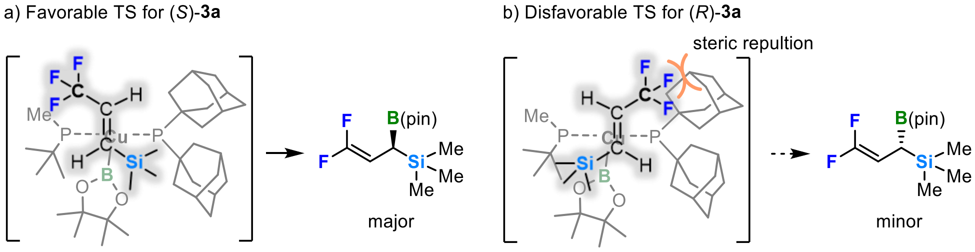


Figure 2. Proposed catalytic cycle.

The proposed transition states (TSs) for the enantio-determining step are described in Figure 3. The proposed interaction between the substrate and ligand is based on Ito's group previous study on the enantioselective borylation reaction use of C_1 symmetric QuinoxP*-type bisphosphine ligand.[25] The trifluoromethyl group, in which one of the fluorine atoms acts as a leaving group, is located at the sterically less hindered region to avoid steric repulsion between the ligand and substrate (Figure 3a). This situation leads to a favorable TS and affords the major enantiomer [(*S*)-**3a**]. On the other hand, there is steric repulsion between the trifluoromethyl group of substrate and adamantyl moiety of ligand in the unfavored TS (Figure 3b). Thus, this steric repulsion suppresses the formation of the disfavored configuration, and (*R*)-**3a** was obtained as the minor enantiomer.


a) Favorable TS for (*S*)-**3a**

b) Disfavorable TS for (*R*)-**3a**

Figure 3. Proposed transition states determining the enantioselectivity of the reaction.

2.3. Conclusions

The development of an enantioselective borylation of trifluoromethyl- and silyl-substituted alkenes were achieved by using a C_1 symmetric QuinoxP*-type bisphosphine ligand. The desired allylboronate products were obtained in good yield with high enantioselectivity. This is the first synthesis of optically active *gem*-difluoro-1-silyl-allylboronates reported before. Not only boron moiety but also silyl groups in the products were derivatized into a variety of functionalities, which show their synthetic utility toward the preparation of structurally complex chiral fluorinated molecules that are difficult to obtain by other synesthetic routes.

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[26] The author observed that the reaction gave the product between 76% ee and 86% ee. The author supposes that this is caused by impurities in the substrate or the catalyst.

[27] Iwamoto, H.; Ozawa, Y.; Takenouchi, Y.; Imamoto, T.; Ito, H. *J. Am. Chem. Soc.* **2021**, *143*, 6413.

[28] Chen, L.-Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 5316.

[29] Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.

[30] Ikeda, A.; Omote, M.; Kusumoto, K.; Tarui, A.; Sato, K.; Ando, A. *Org. Biomol. Chem*. **2015**, *13*, 8886.

[31] The author used a different batch of allylboronate (*S*)-3a with 76% ee for the Sonogashira coupling.

2.5. Experimental details

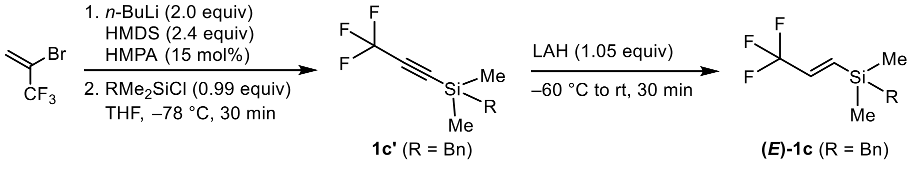
2.5.1. Instrumentation and Chemicals

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4A). NMR spectra were recorded on JEOL JNM-ECX400P, JNM-ECS400, JNM-ECA400, and JNM-ECB400 spectrometers (^{1}H: 400 MHz, ^{13}C: 100 MHz, and ^{19}F: 373 MHz). Tetramethylsilane (^{1}H, δ 0.00), $CDCl_3$ (^{13}C, δ 77.0), and fluorobenzene (^{19}F, δ –113.60) were employed as the external standards, respectively. Fluorobenzene was used as an internal standard to determine ^{19}F NMR yield. CuCl (ReagentPlus® grade, 224332-25G, ≥99%) was purchased from Sigma-Aldrich Co. and used as received. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with a ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and an FID detector. Recycle preparative gel chromatography (GPC) was conducted with LaboACE LC-5060 Series using $CHCl_3$ as an eluent. HPLC analyses with chiral stationary phase were carried out using a Hitachi LaChrome Elite HPLC system with an L-2400 UV detector and a Hitachi chromaster HPLC system with a 5430 diode array detector. Specific optical rotations were measured with HORIBA SEPA-300 and JASCO: P-2200. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University. Single crystal X-ray structural analysis was carried out on a Rigaku XtaLAB PRO MM007 diffractometer using graphite monochromated CuK_α radiation. The structure was solved by direct methods and expanded using Fourier techniques. Nonhydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. All calculations were performed using the Olex2 crystallographic software package except for refinement, which was performed using SHELXL. [1]

2.5.2. Substrate Preparation Procedures

Each silyl-group substituted alkenes [(*E*)-**1b**, (*E*)-**1c**] were prepared according to the references. (*E*)-**1c** was characterized as described below. Spectroscopic data of known compounds **1b’** and (*E*)-**1b** were matched with those of the reported ones.[2, 3]

2.5.2.1. Preparation of (*E*)-1c.[3]

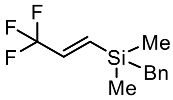


A vacuum-dried 100 mL round-bottomed flask was charged with THF (10 mL) and cooled to 0 °C under N_2 atmosphere. Hexamethyldisilazane (1.75 mL, 8.57 mmol, 2.4 equiv), HMPA (90 μL, 0.5 mmol), and *n*-BuLi (1.6 M in hexane, 5.5 mL, 7.15 mmol, 2.0 equiv) were added to the flask at 0°C. After the addition was complete, the mixture was allowed to cool to –78 °C and stirred for 15 min. Another vacuum-dried 50 mL round-bottomed flask was charged with THF (3 mL) and cooled to 0 °C under N$_2$ atmosphere. 2-Bromo-3,3,3-trifluoropropene (0.4 mL, 3.93 mmol, 1.1 equiv) was added to the flask at 0°C. After the addition was complete, the mixture was allowed to cool to –78 °C and stirred for 15 minutes. This solution was transferred to a solution of HMDS, HMPA, and *n*-BuLi at –78 °C by cannula. After the addition, the mixture was allowed to stir at –78 °C for 30 min. Benzylchlorodimethylsilane (0.65 mL, 3.59 mmol) was added to the mixture and stirred for 30 minutes at –78 °C. After 30 minutes, hexane (35 mL) was added to the mixture at –78 °C and allowed to warm to room temperature. The reaction was quenched by adding a saturated solution of NH$_4$Cl (15 mL), and the mixture was extracted with hexane. The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The dark-brown oil residue was subjected to Kugelrohr under the reduced pressure to afford the corresponding alkyne as a colorless oil [Kugelrohr distillation: 5.5×10^{-1} hPa, 40–50 °C, 66% yield (571.8 mg, 2.36 mmol)].

^{1}H NMR (401 MHz, CDCl$_3$): δ 0.19 (s, 6H), 2.25 (s, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 7.2 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (99 MHz, CDCl$_3$): δ –3.21 (*C*H$_3$), 24.9 (*C*H$_2$), 91.0 (q, *J* = 50.0 Hz, *C*), 92.7 (d, *J* = 4.7 Hz, *C*), 113.1 (q, *J* = 256.3 Hz, *C*H), 128.3 (*C*H), 128.5 (*C*H), 137.3 (*C*). ^{19}F NMR (377 MHz, CDCl$_3$): δ –51.7 (s, 3F). HRMS–EI (*m*/*z*): [M]$^+$ calcd for $C_{12}H_{13}F_3Si$, 242.0739; found, 242.0739.

In a vacuum-dried 100 mL round-bottomed flask, LAH (87.6 mg, 2.31 mmol) was dissolved in THF (10 mL) under N$_2$ atmosphere and allowed to cool to –60 °C and stirring for 15 min. **1c'** (532.6 mg, 2.2 mmol) was added to the mixture at –60 °C and allowed to warm to rt, and stirred for 30 minutes. Then, the mixture was allowed to cool to –30 °C. The mixture was quenched with water and stirred for 30 minutes at –60 °C. The mixture was extracted with ether and dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The colorless oil residue was purified by flash column chromatography (SiO$_2$, hexane only) to furnish the corresponding alkene (*E*)-**1c** (249.0 mg, 1.02 mmol, 46% yield)as a colorless oil.

2.5.2.2. (*E*)-Benzyldimethyl(3,3,3-trifluoroprop-1-en-1-yl)silane [(*E*)-1c].



(*E*)-**1c**

(*E*)-**1c** was prepared from the corresponding alkyne according to the procedure described above. (*E*:*Z* = >95:5, determined by GC analysis)

^{1}H NMR (392 MHz, CDCl$_3$): δ 0.10 (s, 6H), 2.17 (s, 2H), 5.94 (dq, *J* = 5.7 Hz, 11.3 Hz, 19.1 Hz, 1H), 6.57 (dq, *J* = 2.0 Hz, 4.0 Hz, 19.1 Hz, 1H), 6.96 (d, *J* = 7.1 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (99 MHz, CDCl$_3$): δ –4.08 (CH$_3$), 25.0 (*C*H$_2$), 122.1 (q, *J* = 272.9 Hz, *C*), 124.5 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 132.0 (q, *J* = 34.4 Hz, *C*H), 138.5 (*C*), 138.7 (q, *J* = 12.3 Hz, *C*H). ^{19}F NMR (369 MHz, CDCl$_3$): δ –66.9 (s, 3F). HRMS–EI (*m*/*z*): [M]$^+$ calcd for $C_{12}H_{15}F_3Si$, 244.0895; found, 244.0898.

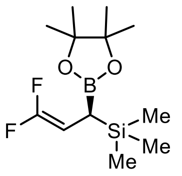
2.5.3. General Borylation Procedures

2.5.3.1. Representative procedure for the copper(I)-catalyzed enantioselective borylation

An oven-dried reaction vial was charged with copper chloride (1.2 mg, 0.0125 mmol),bis(pinacolato)diboron (95.2 mg, 0.375 mmol), (*S*)-Quinox-*t*BuAd$_2$ (6.7 mg, 0.0125 mmol) and transferred to an argon-filled glove box. After NaOMe (20.2 mg, 0.375 mmol) was added to the vial, it was capped with a rubber septum and removed from the glovebox. The solids were suspended in THF (500 µL), and the suspension was allowed to stir for 10 min at 0 ºC. (*E*)-**1** (42.0 mg,0.25 mmol) was added to the suspension, and the mixture was allowed to warm to 30 ºC immediately and stirred until full consumption of starting material was observed. Subsequently, the mixture was passed through a short plug of silica gel (Φ: 10 mm, the height of the silica gel column: 30 mm), eluted with Et_2O, and the volatiles were removed in vacuo. The resulting oily residue was subjected to silica gel chromatography (Et_2O/hexane, typically 0:100–4:96) to give the corresponding borylation product (*S*)-**3** as a colorless oil. Racemic products for HPLC analysis were also synthesized with (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphane) (Xantphos) replacing (*S*)-Quinox-*t*BuAd$_2$.

2.5.4. Characterization of Borylation Product

2.5.4.1. (*S*)-[3,3-Difluoro-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]trimethyl silane [(*S*)-3a].

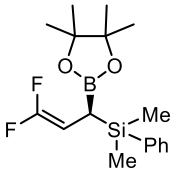


(*S*)-**3a**

The reaction was conducted for 27 h with 42.0 mg (0.25 mmol) of (*E*)-**1a**. The product (*S*)-**3a** was obtained in 77% yield (49.9 mg, mmol) with 86% ee.

^{1}H NMR (392 MHz, $CDCl_3$): δ 0.07 (s, 9H), 1.24 (s, 12H), 1.33 (d, *J* = 11.3 Hz, 1H), 4.27 (ddd, *J* = 2.6, 11.7, 25.8 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$): δ –1.83 (*C*H_3), 10.4 (br, B–*C*H), 24.88 (*C*H_3), 24.90 (*C*H), 75.9 (t, *J* = 23.2 Hz, *C*H), 83.2 (*C*), 154.7 (t, *J* = 284.2 Hz, *C*). ^{19}F NMR (369 MHz, $CDCl_3$): δ –95.2 – –94.8 (m, 1F), –93.1 – –92.7 (m, 1F) HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{23}BF_2O_2Si$, 275.1565; found, 275.1575. $[\alpha]_D{}^{23}$ –6.02 (c 1.06, $CHCl_3$). The ee value was determined by HPLC analysis of the corresponding allylboration product. Daicel CHIRALPAK® IA, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *R* isomer: t_R = 24.51 min., *S* isomer: t_S = 30.32 min.

2.5.4.2. (*S*)-[3,3-Difluoro-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]dimethyl(phenyl)silane [(*S*)-3b].

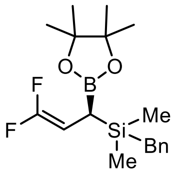


(*S*)-**3b**

The reaction was conducted at 30 ºC from the beginning and stirred at 30 ºC for 8 h with 57.3 mg (0.25 mmol) of (*E*)-**1b.** The product (*S*)-**3b** was obtained in 80% yield (51.2 mg, 0.204 mmol) with 84% ee.

^{1}H NMR (392 MHz, CDCl$_3$): δ 0.36 (s, 3H), 0.37 (s, 3H), 1.14 (s, 6H), 1.15 (s, 6H), 1.19 (d, *J* = 3.1 Hz, 1H), 4.25 (ddd, *J* = 2.5, 11.6, 25.5 Hz, 1H), 7.31–7.37 (m, 3H), 7.49–7.55 (m, 2H). ^{13}C NMR (99 MHz, CDCl$_3$): δ –3.17 (CH$_3$), 9.61 (br, B–*C*H), 24.8 (*C*H$_3$), 75.6 (t, *J* = 23.1 Hz, *C*H), 83.3 (*C*), 127.6 (*C*H), 129.2 (*C*H), 133.8 (*C*H), 137.4 (*C*), 154.8 (t, *J* = 286.1 Hz, *C*). ^{19}F NMR (369 MHz, CDCl$_3$): δ -94.7– –93.8 (m, 1F), –92.6– –91.9 (m, 1F). HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{17}H_{25}BO_2F_2SiNa$, 360.1614; found, 360.1611. $[\alpha]_D^{20}$ –5.07 (c 1.08, CHCl$_3$). The ee value was determined by HPLC analysis of the corresponding allylboration product. Daicel CHIRALPAK® IB, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40 °C, *S* isomer: t_S = 17.60 min., *R* isomer: t_R = 20.29 min.

2.5.4.3. (*S*)-[3,3-Difluoro-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]dimethyl(benzyl)silane [(*S*)-3c].



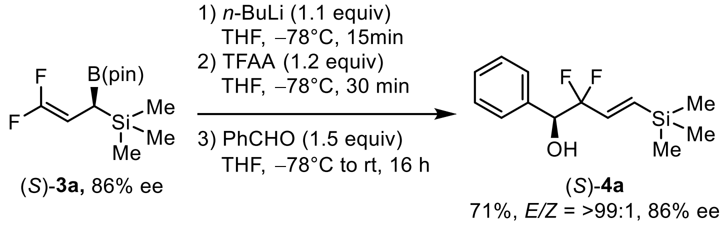
(*S*)-**3c**

The reaction was conducted at 30 ºC and stirred at 30 ºC for 20 h with 61.5 mg (0.25 mmol) of (*E*)-**1c.** The product (*S*)-**3c** was obtained in 74% yield (65.2 mg, 0.185 mmol) with 82% ee.

^{1}H NMR (392 MHz, CDCl$_3$): δ 0.004 (s, 3H), 0.013 (s, 3H), 1.255 (s, 6H), 1.258 (s, 6H), 1.41 (dd, *J* = 1.6 Hz, 11.8 Hz, 1H), 2.167 (s, 1H), 2.171 (s, 1H), 4.28 (ddd, *J* = 2.5, 11.6, 25.7 Hz, 1H), 6.96–7.12 (m, 3H), 7.12 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (99 MHz, CDCl$_3$): δ –4.04 (*C*H$_3$), –3.83 (*C*H$_3$), 8.82 (br, B-*C*H), 24.9 (*C*H$_3$), 25.0 (*C*H$_3$), 75.6 (t, *J* = 23.1 Hz, *C*H), 83.4 (*C*), 124.1 (*C*H), 128.2 (*C*H), 139.5 (*C*), 154.7 (t, *J* = 282.3 Hz, *C*). ^{19}F NMR (369 MHz, CDCl$_3$): δ –94.4– –93.8 (m, 1F), –92.5 – –92.0 (m, 1F). HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{18}H_{27}BO_2F_2SiNa$, 374.1770; found, 374.1766. $[\alpha]_D^{21}$ –12.72 (c 1.04, CHCl$_3$). The ee value was determined by HPLC analysis of the corresponding allylboration product. Daicel CHIRALPAK® IB 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40 °C, *S* isomer: t_S = 21.10 min., *R* isomer: t_R = 22.85 min.

2.5.5. Allylation of Aldehydes with *gem*-Difluoroallylboronates

2.5.5.1. Allylation reaction between (*S*)-3a and benzaldehyde.[4]



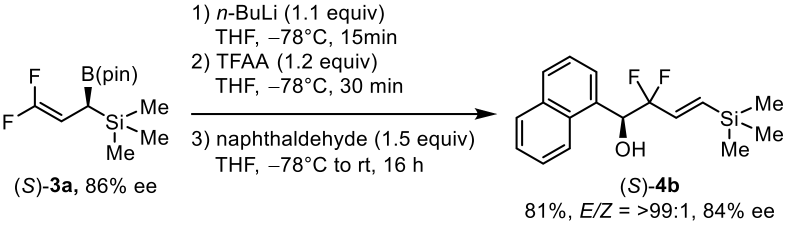
(*S*)-**3a**, 86% ee

(*S*)-**4a**
71%, *E/Z* = >99:1, 86% ee

In an oven-dried reaction vial, a solution of (*S*)-**3a** (19.9 mg, 0.07 mmol) in THF (724 µL) was treated with *n*-BuLi in hexane (1.55 M, 49.8 µL, 0.077 mmol) at –78°C and the solution was stirred for 15 min. Trifluoroacetic anhydride (12 µL, 0.084 mmol) was then added dropwise to this mixture, and the reaction was stirred for a further 30 min at –78°C. Benzaldehyde (11 µL, 0.105 mmol) was then added at –78°C, and the mixture was allowed to warm up to room temperature. After 16 hours, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4. After the filtration, the solvent was removed. The crude material was purified by flash column chromatography (SiO_2, EtOAc/hexane, 3:97–8:92) to give the corresponding (*S*)-**4a** (13.2 mg, 0.051 mmol, 71%) as a colorless oil with 86% ee. The stereoselectivity of (*S*)-**4a** was determined by ^{1}H NMR analysis (*E/Z* = >99:1).

^{1}H NMR (401 MHz, $CDCl_3$): δ 0.05 (s, 9H), 2.45 (d, *J* = 3.6 Hz, 1H), 4.90 (dt, *J* = 2.4, 9.4 Hz, 1H), 5.95 (dt, *J* = 4.8, 15.0 Hz, 1H), 6.21 (dt, *J* = 3.9, 10.8 Hz, 1H), 7.42–7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –1.85 (*C*H_3), 76.0 (t, *J* = 19.3 Hz, *C*H), 119.4 (t, *J* = 252.6 Hz, *C*), 127.7 (*C*H), 128.0 (*C*H), 128.6 (*C*H), 135.2 (t, *J* = 26.2 Hz, *C*H), 136.1 (*C*), 138.5 (t, *J* = 5.7 Hz, *C*H). ^{19}F NMR (377 MHz, $CDCl_3$): δ –110.4– –108.2 (m, 2F). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{18}OF_2SiNa$, 279.0987; found, 279.0980. $[\alpha]_D^{24}$ +19.6 (c 0.61, $CHCl_3$). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® IA, 2-PrOH/hexane = 2:98, 0.5 mL/min, 40 °C, *R* isomer: t_R = 20.38 min., *S* isomer: t_S = 24.93 min.

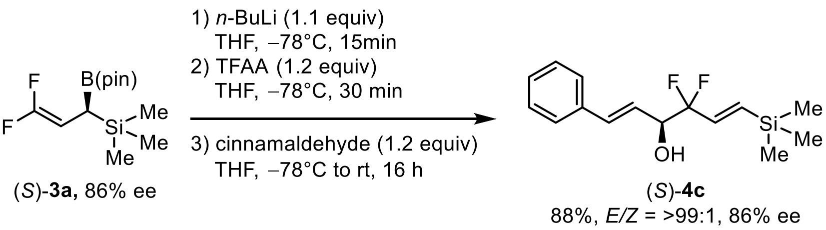
2.5.5.2. Allylation reaction between (*S*)-3a and naphthaldehyde.



The reaction was conducted with 20.3 mg (0.072 mmol) of (*S*)-**3a**. The title compound was purified by flash column chromatography (SiO_2, EtOAc/hexane, 3:97–8:92) and gel permeation chromatography. The compound (*S*)-**4b** was obtained in 81% isolated yield (16.6 mg, 0.060 mmol) with 84% ee as a colorless oil. The stereoselectivity of (*S*)-**4b** was determined by ^{1}H NMR analysis (*E/Z* = >99:1).

^{1}H NMR (401 MHz, $CDCl_3$): δ –0.03 (s, 9H), 2.59 (d, *J* = 3.2 Hz, 1H), 5.81 (dt *J* = 1.9, 9.0 Hz, 1H), 5.97 (dt, *J* = 5.0, 15.1 Hz, 1H), 6.20 (dt, *J* = 3.8, 10.5 Hz, 1H), 7.45–7.56 (m, 3H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.87 (t, *J* = 7.6 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –1.9 (CH_3), 71.7 (t, *J* = 30.1 Hz, *C*H), 120.0 (t, *J* = 245.7 Hz, *C*), 123.6 (*C*H), 125.0 (*C*H), 125.5 (*C*H), 126.1 (*C*H), 126.2 (*C*H), 128.8 (*C*H), 129.3 (*C*H), 131.3 (*C*), 132.2 (*C*), 133.5 (*C*), 135.4 (t, *J* = 26.3 Hz, *C*H), 138.2 (t, *J* = 6.1 Hz, *C*H). ^{19}F NMR (377 MHz, $CDCl_3$): δ –108.4 (s, 2F). HRMS-EI (m/z): $[M+H]^+$ calcd for $C_{17}H_{20}OF_2Si$, 306.1252; found, 306.1259. $[\alpha]_D{}^{23}$ +57.9 (c 0.38, $CHCl_3$). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® IB, 2-PrOH/hexane = 1:99, 0.5 mL/min, 40 °C, *R* isomer: t_R = 21.17 min., *S* isomer: t_S = 24.17 min.

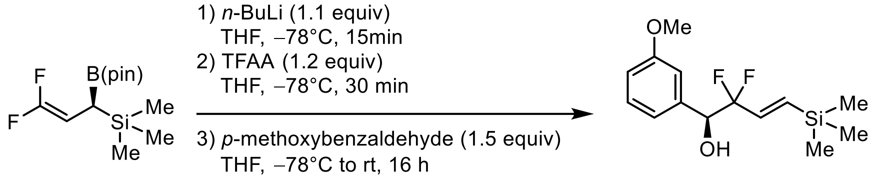
2.5.5.3. Allylation reaction between (*S*)-3a and cinnamaldehyde.



The reaction was conducted with 19.9 mg (0.072 mmol) of (*S*)-**3a**. The title compound was purified by flash column chromatography (SiO_2, EtOAc/hexane, 3:97–8:92) and gel permeation chromatography. The compound (*S*)-**4c** was obtained in 88% isolated yield (16.6 mg, 0.060 mmol) with 86% ee as a colorless oil. The stereoselectivity of (*S*)-**4c** was determined by ^{1} H NMR analysis (*E/Z* = >99:1).

^{1}H NMR (401 MHz, $CDCl_3$): δ 0.11 (s, 9H), 2.15 (d, *J* = 5.6 Hz, 1H), 4.49 (septet, *J* = 5.0 Hz, 1H), 6.04–6.22 (m, 2H), 6.45 (dt, *J* = 3.8, 10.7 Hz, 1H), 6.75 (d, *J* = 16.0 Hz, 1H), 7.27–7.31 (m, 1H), 7.31–7.37 (m, 2H), 7.38–7.42 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$): δ –1.74 (CH_3), 74.5 (t, *J* = 30.7 Hz, *C*H), 119.2 (t, *J* = 246.5 Hz, *C*), 123.4 (*C*H), 126.7 (*C*H), 128.2 (*C*H), 128.6 (*C*H), 134.5 (*C*H), 135.4 (t, *J* = 26.4 Hz, *C*H), 136.0 (*C*), 138.5 (t, *J* = 5.7 Hz, *C*H). ^{19}F NMR (377 MHz, $CDCl_3$): δ –111.3– –108.0 (m, 2F). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{20}OF_2SiNa$, 305.1144; found, 305.1140. $[\alpha]_D{}^{26}$ –6.18 (c 1.0, $CHCl_3$). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® IA, 2-PrOH/hexane = 2:98, 0.5 mL/min, 40 °C, *S* isomer: t_S = 24.97 min, *R* isomer: t_R = 28.95 min.

2.5.5.4. Allylation reaction between (*S*)-3a and *p*-methoxybenzaldehyde.



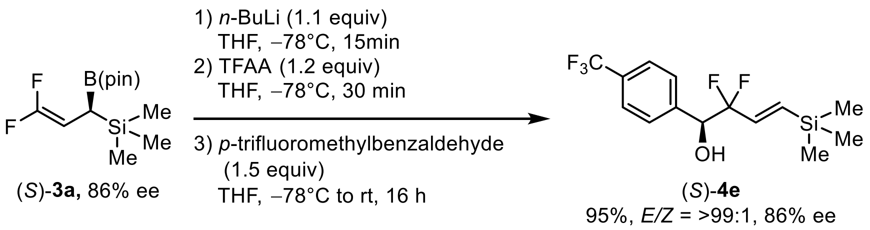
(*S*)-**3a,** 86% ee

(*S*)-**4d**
82%, *E/Z* = >99:1, 82% ee

The reaction was conducted with 20.1 mg (0.071 mmol) of (*S*)-**3a**. The title compound was purified by flash column chromatography (SiO_2, EtOAc/hexane, 3:97–8:92) and gel permeation chromatography. The compound (*S*)-**4d** was obtained in 82% isolated yield (15.4 mg, 0.060 mmol) with 82% ee as a colorless oil. The stereoselectivity of (*S*)-**4d** was determined by ^{1}H NMR analysis (*E/Z* = >99:1).

^{1}H NMR (401 MHz, $CDCl_3$): δ 0.06 (s, 9H), 2.45 (d, *J* = 3.6 Hz, 1H), 3.81 (s, 3H), 4.88 (td, *J* = 2.0, 9.5 Hz, 1H), 5.95 (dt, *J* = 4.9, 14.9 Hz, 1H), 6.24 (td, *J* = 3.4, 10.8 Hz, 1H), 6.88 (dd, *J* = 2.4, 8.0 Hz, 1H), 6.92–6.98 (m, 2H), 7.22–7.30 (m, 1H) ^{13}C NMR (99 MHz, $CDCl_3$): δ –1.82 (*C*H_3), 55.2 (*C*H_3), 75.9 (t, *J* = 30.7 Hz, *C*H), 113.0 (*C*H), 114.3 (*C*H), 119.3 (t, *J* = 247.0 Hz, *C*), 120.0 (*C*H), 129.1 (*C*H), 135.2 (t, *J* = 26.4 Hz, *C*H), 137.6 (*C*), 138.4 (t, *J* = 6.1 Hz, *C*H). ^{19}F NMR (377 MHz, $CDCl_3$): δ –109.6– –107.5 (m, 2F). HRMS-EI (m/z): $[M]^+$ calcd for $C_{14}H_{20}O_2F_2Si$, 286.1201; found, 286.1205. $[\alpha]_D^{25}$ +8.59 (c 0.83, $CHCl_3$). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® IC, 2-PrOH/hexane = 3:97, 0.5 mL/min, 40 °C, *R* isomer: t_R = 16.24 min, *S* isomer: t_S = 17.84 min.

2.5.5.5. Allylation reaction between (*S*)-3a and *p*-trifluoromethylbenzaldehyde



(*S*)-**3a,** 86% ee

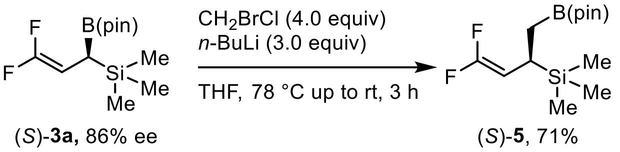
(*S*)-**4e**
95%, *E/Z* = >99:1, 86% ee

The reaction was conducted with 20.2 mg (0.071 mmol) of (*S*)-**3a**. The title compound was purified by flash column chromatography (SiO$_2$, EtOAc/hexane, 3:97–8:92) and gel permeation chromatography. The compound (*S*)-**4e** was obtained in 95% isolated yield (17.9 mg, 0.07 mmol) with 86% ee as a colorless oil. The stereoselectivity of (*S*)-**4e** was determined by ^{1}H NMR analysis (*E/Z* = >99:1).

^{1}H NMR (401 MHz, CDCl$_3$): δ 0.05 (s, 9H), 2.54 (d, *J* = 3.6 Hz, 1H), 4.98 (td, *J* = 2.1, 9.0 Hz, 1H), 5.86–6.00 (m, 1H), 6.20 (dt, *J* = 3.8, 10.8 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H) ^{13}C NMR (99 MHz, CDCl$_3$): δ –1.88 (*C*H$_3$), 75.4 (td, *J* = 5.3, 31 Hz, *C*H), 119.1 (t, *J* = 247.0 Hz, *C*), 123.9 (q, *J* = 270.0 Hz, *C*H), 124.9 (*C*H), 128.0 (*C*H), 130.8 (q, *J* =32.0 Hz, *C*), 134.5 (t, *J* = 26.0 Hz, *C*H), 138.7 (d, *J* = 104.0 Hz, *C*H), 139.9 (*C*). ^{19}F NMR (377 MHz, CDCl$_3$): δ –110.7– –107.1 (m, 2F), –63.4 (s, 3F). HRMS-ESI (m/z): [M]$^-$ calcd for C$_{14}$H$_{16}$OF$_5$Si, 323.0896; found, 323.0896. [α]$_D$ ^{25} +11.3 (c 0.71, CHCl$_3$). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® IB, 2-PrOH/hexane = 2:98, 0.5 mL/min, 40 °C, *S* isomer: *R* isomer: t$_R$ = 16.10 min, t$_S$ = 17.09 min.

2.5.6. Derivatization of *gem*-Difluoroallylboronates

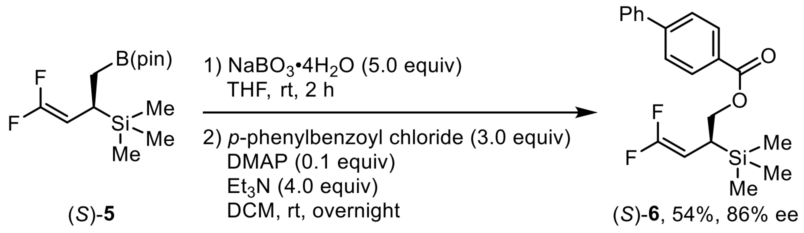
2.5.6.1. Procedure for the homologation of (*S*)-3a.



The homologation was performed according to the literature procedure.[5] In a reaction vial, the borylation product (0.14 mmol) was typically dissolved in THF (1080 μL). CH_2BrCl (0.56 mmol, 19.4 μL) was then added to the vial at room temperature. Then, the mixture was allowed to cool to –78 ºC and stirred 15 minutes. *n*-BuLi (0.42 mmol, 1.6 M in hexane, 135 μL) was added dropwise to the mixture at –78 ºC. After being stirred for 30 minutes, the reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was dried over Na_2SO_4. After filtration, the crude mixture was purified by flash column chromatography (SiO_2, ether/hexane, typically 0:100–4:96). (*S*)-**5** was obtained in 71% yield as a colorless oil.

^{1}H NMR (401 MHz, $CDCl_3$): δ –0.02 (s, 9H), 0.73 (dd, *J* = 11.0, 14.5 Hz, 1H), 0.96 (ddd, *J* = 2.2, 4.2, 15.4 Hz, 1H), 1.23 (s, 6H), 1.25 (s, 6H), 1.66–1.77 (m, 1H), 4.00 (ddd, *J* = 3.1, 11.5, 25.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –3.65 (CH_3), 11.10 (br, B–*C*H), 17.2 (*C*H), 24.8 (d, *J* = 36.0 Hz, *C*H_3), 80.8 (t, *J* = 20.6 Hz, *C*H), 83.2 (*C*), 155.3 (t, *J* = 284.0 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –92.9—92.4 (m, 1F), –92.0—91.6 (m, 1F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{25}BO_2F_2Si$, 289.1721; found, 289.1712. $[\alpha]_D{}^{21}$ +4.66 (c 0.54, $CHCl_3$).

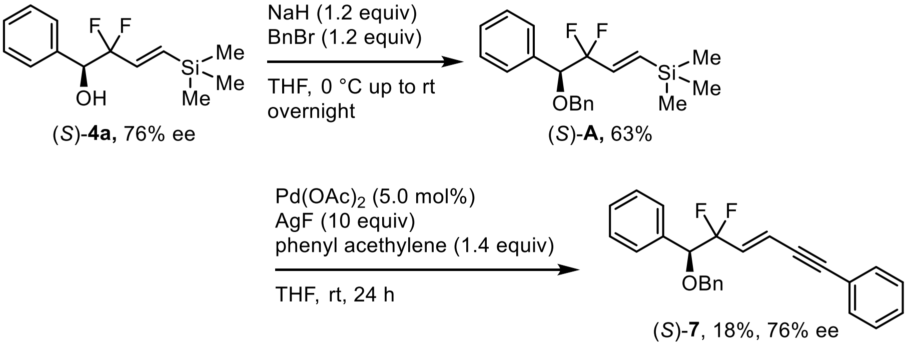
2.5.6.2. Procedure for the oxidation and acylation of (*S*)-5.



In a reaction vial, (*S*)-**5** (19.8 mg, 0.068 mmol) was dissolved in THF/H_2O (1:1, 2.0 mL). $NaBO_3{\cdot}4H_2O$ (52.9 mg, 0.34 mmol) was then added to the vial at room temperature. After stirring for 2 hours, the reaction mixture was extracted with Et_2O. The organic layer was dried over Na_2SO_4. After filtration, the volatiles were removed in vacuo at 0 ºC. The resulting volatile oily residue was used in the next step without purification. After the crude alcohol mixture was transferred into a reaction vial, the vial was filled up with N_2 gas. Then, DCM (1 mL), Et_3N (28.4 mg, 0.27 mmol, 4.0 equiv), DMAP (2.0 mg, 0.0068 mmol, 0.1 equiv) and *p*-phenylbenzoyl choloride (43.3 mg, 0.2 mmol, 3.0 equiv) were added to the vial and stirred at room temperature for overnight. The reaction was quenched by the addition of H_2O, and the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4. After filtration, the crude product was purified by flash column chromatography (SiO_2, EtOAc/hexane, typically 1:99–5:95). (*S*)-**6** was obtained in 54% two steps yield as a white solid with 86% ee.

^{1}H NMR (401 MHz, $CDCl_3$): δ 0.13 (s, 9H), 2.19 (t, *J* = 10.4 Hz, 1H), 4.18 (ddd, *J* = 1.9 , 4.1, 10.8 Hz, 1H), 4.32 (t, *J* = 10.8 Hz, 1H), 4.49 (ddd, *J* = 1.9, 4.1, 10.9 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.65 (dd, *J* = 8.0, 16.0 Hz, 4H), 8.09 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -2.95 (CH_3), 24.1 (*C*H), 65.6 (*C*H), 77.0 (t, *J* = 22.0 Hz, *C*H), 127.1 (*C*H), 127.3 (*C*H), 128.1 (*C*H), 128.9 (*C*H), 130.0 (*C*H), 140.0 (*C*), 145.7 (C), 156.3 (t, *J* = 290.0 Hz, *C*), 166.6 (C). ^{19}F NMR (377 MHz, $CDCl_3$): δ –92.3—91.6 (m, 1F), –89.3—88.6 (m, 1F) HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{22}F_2O_2SiNa$, 383.1249; found, 383.1241. $[\alpha]_D{}^{24}$ +7.78 (c 0.79, $CHCl_3$). The ee value was determined by HPLC analysis of the corresponding allylboration product. Daicel CHIRALPAK® IB 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_S = 12.15 min., *R* isomer: t_R = 13.59 min.

2.5.6.3. Procedure for the protection and cross-coupling of (*S*)-4a



The protection was performed according to the literature procedure.[6] In a reaction vial, (*S*)-**4a** (131.3 mg, 0.512 mmol, 76% ee) was dissolved in THF (1.00 mL) and allowed to cool to 0 ºC for 10 minutes. NaH (14.69 mg, 0.614 mmol) was added to the vial at 0 ºC. After being stirred for 1 hour, BnBr (105.2 mg, 0.614 mmol) was added dropwise to this mixture over 30 minutes, and the reaction was allowed to warm to room temperature overnight. The reaction was quenched by the addition of H_2O at 0 ºC, and the mixture was extracted with Et_2O. The organic layer was dried over with Na_2SO_4. After the filtration, the crude mixture was purified by flash column chromatography (SiO_2, CH_2Cl_2/hexane, typically 1:99–20:80). The protected compound [(*S*)-**A**] was obtained in 111.2 mg, 63% as a pale-yellow oil.

^{1}H NMR (392 MHz, $CDCl_3$): δ 0.08 (s, 9H), 4.36 (d, *J* = 12.2 Hz, 1H), 4.47–4.59 (m, 1H), 4.66 (d, *J* = 12.2 Hz, 1H), 6.00–6.26 (m, 2H), 7.27–7.42 (m, 10H). ^{13}C NMR (99 MHz, $CDCl_3$): δ –1.76 (CH_3), 70.9 (CH_2), 81.8 (t, *J* = 30.2 Hz, *C*H), 118.6 (t, *J* = 245.5 Hz, *C*), 127.8 (*C*H), 128.1 (*C*H), 128.4 (*C*H), 128.7 (*C*H), 134.5 (d, *J* = 2.0 Hz, *C*), 136.3 (t, *J* = 25.9 Hz, *C*H), 137.2 (t, *J* = 6.1 Hz, *C*H), 137.3 (*C*). ^{19}F NMR (369 MHz, $CDCl_3$): δ –104.6 (d, *J* = 239.1 Hz, 1F), –110.8 (d, *J* = 239.5 Hz, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{24}F_2ONaSi$, 369.1457; found, 369.1450. $[\alpha]_D{}^{20}$ +62.12 (c 1.0, $CHCl_3$).

The oxidative Sonogashira cross-coupling was performed based on the modified procedure.[7] $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) was placed in an oven-dried reaction vial. The vial was moved to an argon-filled glovebox. AgF (266.4 mg, 2.1 mmol) was placed in a reaction vial. Then the vial was capped with a rubber septum and removed from the glovebox, and dry MeCN (1.0 mL) was added to the vial through the septum using a syringe.

The protected compound [(*S*)-**A**] (72.2 mg, 0.21 mmol) in MeCN (0.8 mL) was added to the mixture at room temperature. Phenyl acetylene (32.0 mg, 0.294 mmol) was added dropwise to this mixture over 20 minutes and stirred for 24 h at room temperature. After the reaction was complete, the reaction mixture was passed through a short silica gel column (Φ: 10 mm, the height of the silica gel column: 30 mm), eluting with Et_2O. The brown-oil material was dissolved in hexane and passed through a short silica gel column (Φ: 10 mm, the height of the silica gel column: 20 mm), eluting with hexane to remove byproducts. The colorless-oil material was purified by GPC. (*S*)-**7** was obtained 14.1 mg, 18% as a colorless oil with 76% ee.

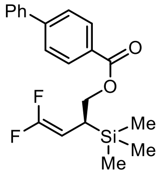
^{1}H NMR (401 MHz, $CDCl_3$): δ 4.42 (d, *J* = 12.4 Hz, 1H), 4.61 (dt, *J* = 5.9, 11.6 Hz, 2H), 6.07–6.30 (m, 2H), 7.27–7.48 (m, 15H). ^{13}C NMR (99 MHz, $CDCl_3$): δ 71.4 (CH_2), 82.2 (t, *J* = 30.7 Hz, *C*H), 85.9 (*C*), 93.7 (*C*), 116.3 (t, *J* = 12.9 Hz, *C*H), 118.8 (t, *J* = 245.0 Hz, *C*), 122.7 (*C*), 127.9 (*C*H), 128.0 (*C*H), 128.43 (*C*H), 128.48 (*C*H), 128.54 (*C*H),128.7 (*C*H), 128.9 (*C*H), 129.0 (*C*H), 131.8 (*C*), 132.7 (t, *J* = 24.9 Hz, *C*H), 134.3 (d, *J* = 3.9 Hz, *C*), 137.3 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –108.7 (d, *J* = 242.8 Hz, 1F), –102.7 (d, *J* = 254.5 Hz, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{20}F_2ONa$, 397.1774; found, 397.1370. $[\alpha]_D{}^{22}$ +74.59 (c 1.28, $CHCl_3$). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® IB 2-PrOH/Hexane = 0/100, 0.5 mL/min, 40 °C, *R* isomer: t_R = 31.53 min., *S* isomer: t_S = 34.36 min.

2.5.6.4. Procedure for the oxidation and esterification of product for the ee determination.

In a reaction vial, the borylation product (0.1 mmol) was dissolved in THF/H_2O (1:1, 1.00 mL), typically. $NaBO_3\cdot 4H_2O$ (76.9 mg, 0.5 mmol) was added to the vial at room temperature. After being stirred for 2 hours, the reaction mixture was extracted with Et_2O. The organic layer was dried over Na_2SO_4. The volatile product was used to the next step without purification. In a reaction vial, the alcohol (0.1 mmol) and DMAP (0.05 mmol) were dissolved in CH_2Cl_2 (1.00 mL), typically. Et_3N (28.0 µL, 0.2 mmol) and *p*-nitrobenzoyl chloride (27.8 mg, 0.15 mmol) were then added to this solution at room temperature. After being stirred for 3 hours, the reaction mixture was passed through a short silica gel column (Φ: 10 mm, the height of the silica-gel column: 30 mm), eluting with Et_2O. The crude material was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, typically 0:100–8:92) to give the corresponding ester as a white solid.

2.5.6.5. Single Crystal X-ray Structural Analysis

The absolute configuration of the product was determined based on an X-ray crystallographic analysis of the compound (*S*)-**6**. The absolute configurations of other borylation products were deduced by this product. The details are summarized in Figure S1 and Table S1. Molecular structure of (*S*)-**6**. Thermal ellipsoids set at 50% probability; hydrogen atoms are omitted for clarity.



(*S*)-**6**

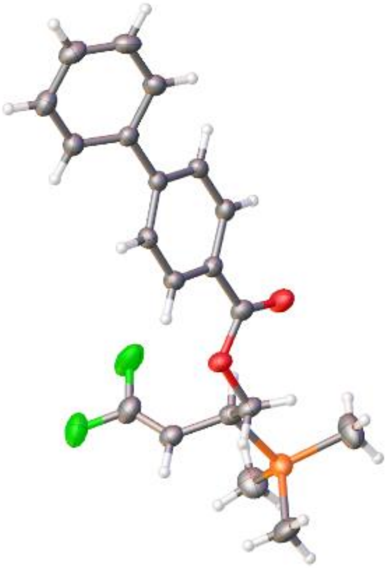


Figure S1. Morecular structure of (*S*)-**6**

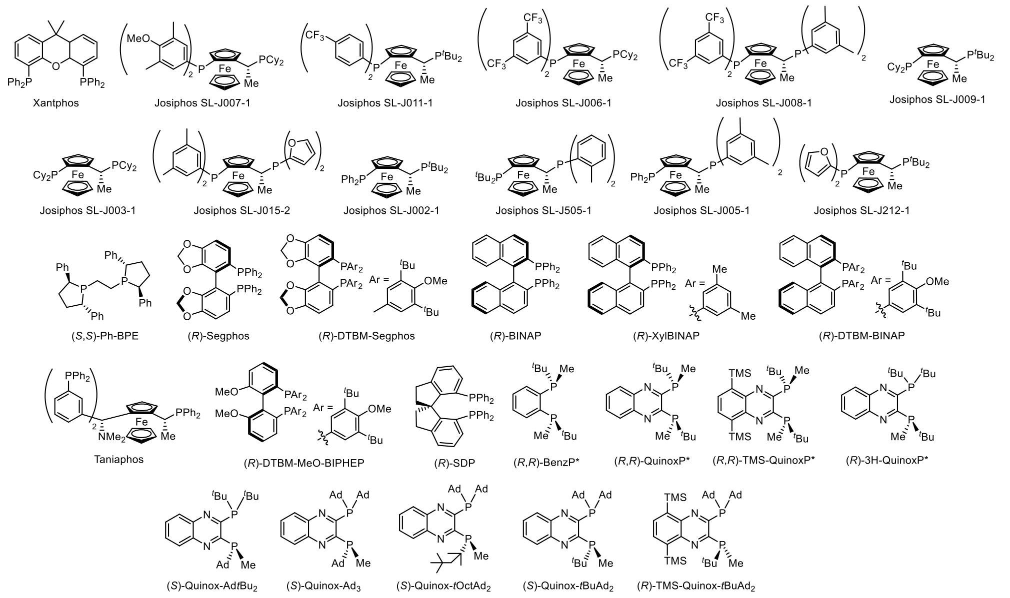
Table S1. Summary of X-ray crystallographic data for (*S*)-**6**.

CCDC number	2157922
Empirical Formula	$C_{20}H_{22}F_2O_2Si$
Formula Weight	360.46
Crystal System	Monoclinic
Crystal Size	0.2×0.15×0.03
a / Å	8.9000(3)
b / Å	6.65969(17)
c / Å	16.0354(4)
α / ^{o}	90
β / ^{o}	90.518(2)
γ / ^{o}	90
V / Å^3	950.40(4)
Space Group	$P2_1$
Z value	2
*D*calc / g cm^{-3}	1.260
Temperature / K	123
No. of Reflections	Total: 8855
Measured	3517 (R_{int} = 0.0222)
Space Group	$P2_1$
Z value	2
*D*calc / g cm^{-3}	1.260
Temperature / K	123
No. of Reflections	Total: 8855
Measured	3517 (R_{int} = 0.0222)
Residuals: R_1 (I > 2.00σ (*I*)) / %	0.0317
Residuals: wR_2 (All reflections) / %	0.0845
Goodness of Fit (GOF)	1.073
Maximum peak in Final Diff. Map / Å3	0.26 e$^-$
Minimum peak in Final Diff. Map / Å3	–0.20 e$^-$
Flack parameter	–0.019(16)

2.5.7. Ligand Investigation

Entry	Ligand (5 mol%)	Time (h)	Isolated yield (%)	% ee
1	Xantophos	2	78	–
2	(*R*, *S*)-Josiphos SL-J007-1	2	79	–48[b]
3	(*R*, *S*)-Josiphos SL-J011-1	2	62	–4[b]
4	(*R*, *S*)-Josiphos SL-J006-1	2	69	–54[b]
5	(*R*, *S*)-Josiphos SL-J008-1	2	83	–34[b]
6	(*R*, *S*)-Josiphos SL-J009-1	8	40	–10
7	(*R*, *S*)-Josiphos SL-J003-1	2	64	14[b]
8	(*S*, *R*)-Josiphos SL-J015-2	2	26	22[b]
9	(*R*, *S*)-Josiphos SL-J002-1	2	68	–18[c]
10	(*R*, *S*)-Josiphos SL-J505-1	10	21	–8[c]
11	(*R*, *S*)-Josiphos SL-J005-1	2	58	–30[b]
12	(*R*, *S*)-Josiphos SL-J212-1	2	64	–36[b]
13	(*S*,*S*)-Ph-BPE	2	73	8[b]
14	(*R*)-Segphos	2	81	–60[b]
15	(*R*)-DTBM-Segphos	2	66	–76[b]
16	(*R*)-BINAP	2	70	–37[c]
17	(*R*)-Xyl-BINAP	2	35	–9[c]
18	(*R*)-DTBM-BINAP	5	59	–24[c]
19	(*R*,*R*)-Taniaphos	2	16	N.D.
20	(*R*)-DTBM-MeO-BIPHEP	6	57	–8[c]
21	(*R*)-SDP	24	N.R.	N.D.
22	(*R*,*R*)-BenzP*	2	68	–76[b]
23	(*R*,*R*)-QuinoxP*	2	23	–72[b]
24	(*R*,*R*)-TMS-QuinoxP*	2	73	–48[c]
25	(*R*)-3H-QuinoxP*	5	32	–66[c]
26	(*S*)-Quinox-Ad*t*Bu$_2$	5	34	74[c]
27	(*S*)-Quinox-Ad$_3$	6	43	84[c]
28	(*S*)-Quinox-*t*OctAd$_2$	8	47	80[c]
29[a]	(*S*)-Quinox-*t*BuAd$_2$	27	77	86[c]
30	(*R*)-TMS-Quinox-*t*BuAd$_2$	8	63	–64[c]

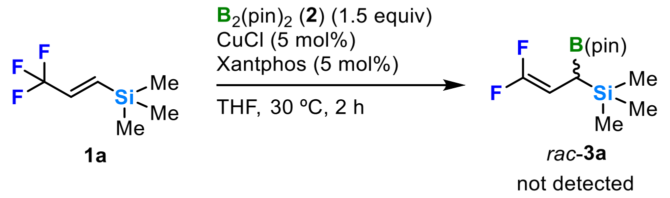
[a] Reaction was conducted at 0℃ for 10 minutes then 30℃. [b] The ee value was determined by HPLC analysis after oxidation and acylation of boronates. [c] The ee value was determined by HPLC analysis after allylboration.



2.5.8. Mechanistic studies

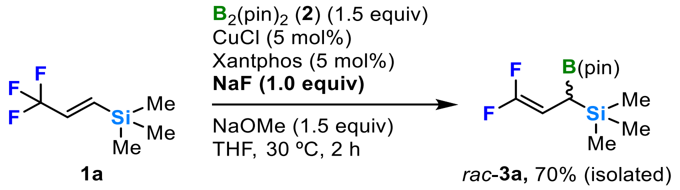
・The reaction in the absence of NaOMe

I investigated the reaction of **1a** without NaOMe in the presence of a CuCl/Xantphos catalyst (the best catalyst for racemic product synthesis), ^{19}F NMR and GC analysis showed that the desired product **3a** was not obtained, and 73% of **1a** remained unreacted. This result suggests that NaOMe is required to form the boryl-copper active species via σ-bond metathesis between in situ formed LCuOMe and bis(pinacolato)diboron.



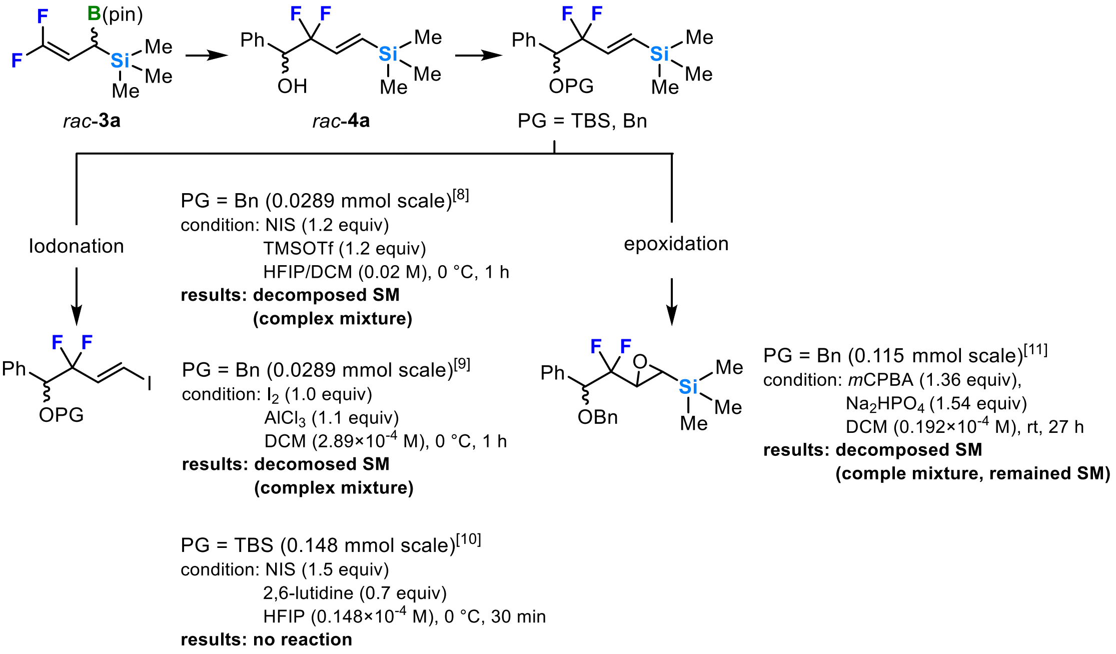
・The reaction in the presence of NaF

I performed the reaction in the presence of NaF (1.0 equiv) to check the effect of NaF. As the result, the desired product 3a was obtained in good yield (70%), comparable to the conditions without NaF (78%). This result suggests that NaF has little to no effect on the product as well as the substrate of the silyl group.



2.5.9. Attempts for other transformations of silyl moiety

I have tried iododesilylation and epoxidation of the derivatives obtained from *rac*-**3a** under various conditions. However, the author was not able to obtain the desired products, as shown below. I considered that fluorine atoms as an electron-withdrawing group could be prejudicial for the reactions.



2.5.10. References

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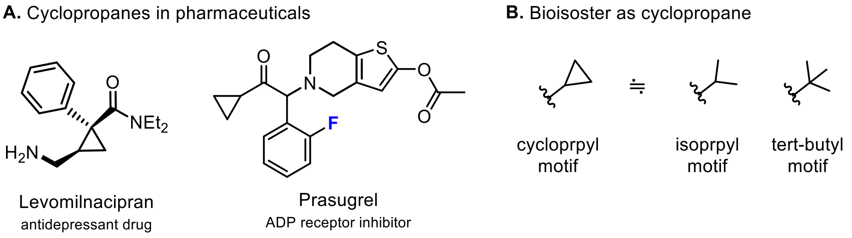
III Synthesis of Fluoromethyl-substituted Cyclopropanes by Electrophilic Cyclization of Homoallylic Boronate Intermediates

3.1. Introduction

Molecules containing cyclopropanes have fascinated researchers. Cyclopropanes have a distorted structure of about 27 kcal/mol associated with such rings, which leads to significant difficulties for their construction, resulting in certain transformations. [1] Cyclopropanes are observed in many areas of organic chemistry, such as total synthesis and pharmaceuticals (Figure 1A). Especially, in pharmaceuticals, cyclopropanes are used as biosiostere and present a well-defined 3-dimensional shape, conformational rigidity, and electronic properties in between that of an alkene and a *gem*-dimethyl group, for instance, because of the small and strained ring structure (Figure 1B). In several decades, researchers developed unique strategies to apply cyclopropanes as key intermediates in routes to access challenging structures, such as medium-sized rings or highly functionalized molecules.


A. Cyclopropanes in pharmaceuticals

B. Bioisoster as cyclopropane

Figure 1. Cyclopropanes in pharmaceuticals and their properties

The numerous powerful strategies to synthesize functionalized cyclopropanes have been extensively investigated; as a typical example, Simmons–Smith cyclopropanation, transition metal-catalyzed carbene insertion to alkenes using diazo compounds, the reaction of sulfur ylides with electron-deficient alkenes, cross-coupling reaction and modified enzyme reaction (Figure 2).[2-5]

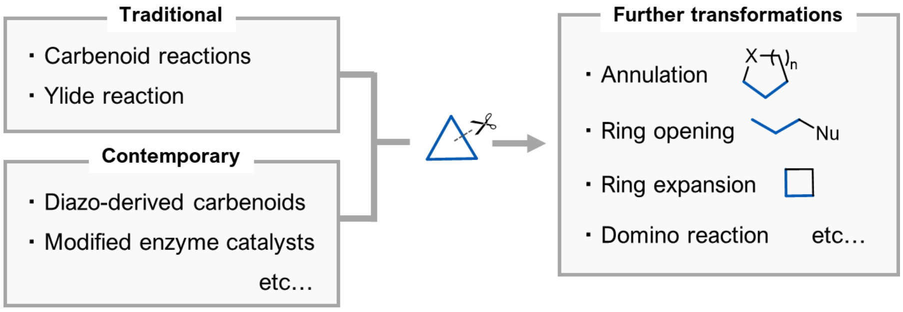


Figure 2. Strategies for the synthesis of functionalized cyclopropanes

As described in general introduction, fluorine atom(s) change the biological properties of pharmaceuticals dramatically because of the electron negativity of fluorine atom(s). Thus, several bioactive compounds have fluorinated cyclopropyl moiety, as described below (Figure 3). Following the background, numerous synthesis methods for that structure, including fluorinated cyclopropyl moiety, are explored to investigate new bioactive compounds in recent years.[6]

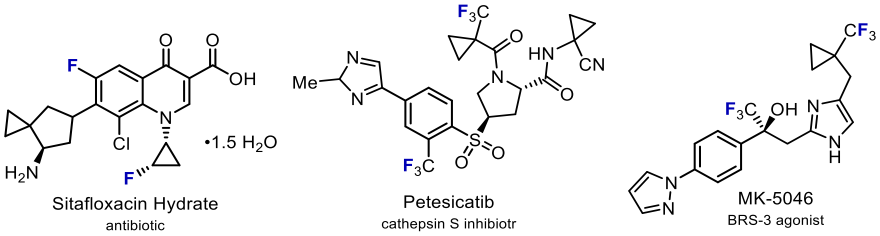


Figure 3. Examples of fluorinated cyclopropane-containing drugs and bioactive compound

Among the strategies to synthesize fluorinated cyclopropyl moiety, there are only seven examples to synthesize cyclopropanes bearing monofluoromethyl group, although there is a lot of strategies to synthesize other fluorinated cyclopropane, e.g., trifluoromethyl group substituted cyclopropanes and monofluorinated cyclopropanes (Figure 4). Examples of currently reported studies include nucleophilic substitution with Tetrabutylammonium tetrafluoroborate, cyclization with active methylene nucleophiles, and addition of carbene intermediates using transition metal catalysis or modified biocatalysts.[7–13]

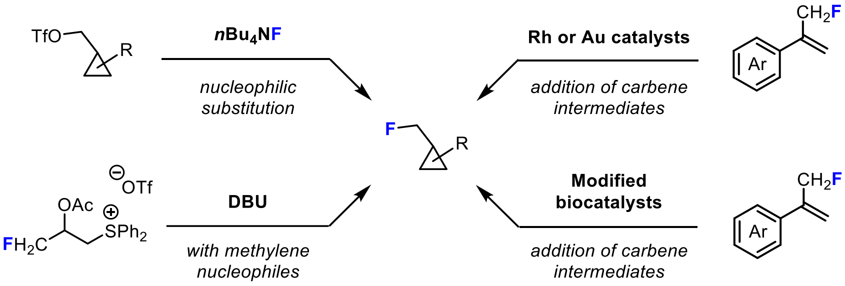


Figure 4. Represent strategies for monofluoromethylated cyclopropanes.

Reactions using boronate complex have long been studied for decades. In 1985, the Matteson group reported the homologation reaction use of optically active secondary organoboron compound and organolithium species. This reaction undergoes a stereospecific1,2-metallation shift when the organolithium species generated in situ coordinates to the vacant p-orbitals of the boron atom (Figure 5A).[14, 15] In recent years, many reactions have been developed using the specific reactivity of these boronate complexes by many groups. [16–18] For instance, the Morken group reported conjunctive cross-coupling of α-substituted alkenyl boronate complexes, activated by lithium reagent in situ and carbamoyl chloride electrophiles to obtain β-boryl amides in 2022 (Figure 5B). [19] Studer group developed radical-polar crossover reactions with the use of vinylboronate via boronate complexes activated by organolithium reagents. The vinyl boron ate complexes act as radical acceptors to form two C–C bonds in the absence of transition metals via radical addition and a subsequent 1,2-R group shift (Figure 5C). [20] In particular, the reaction using the reactivity of boronate complexes was reconfirmed by the Aggarwal group. They established the lithiation–barylation methodology to synthesize many molecules containing multiple contiguous stereogenic centers with exquisite 3-D control via boronate complex in 2010.[21, 22] Moreover, they found that this reaction has been widely used in the sequential modular synthesis strategy, what we call assembly line synthesis, to construct highly stereocontrolled natural products (Figure 5D).[23]

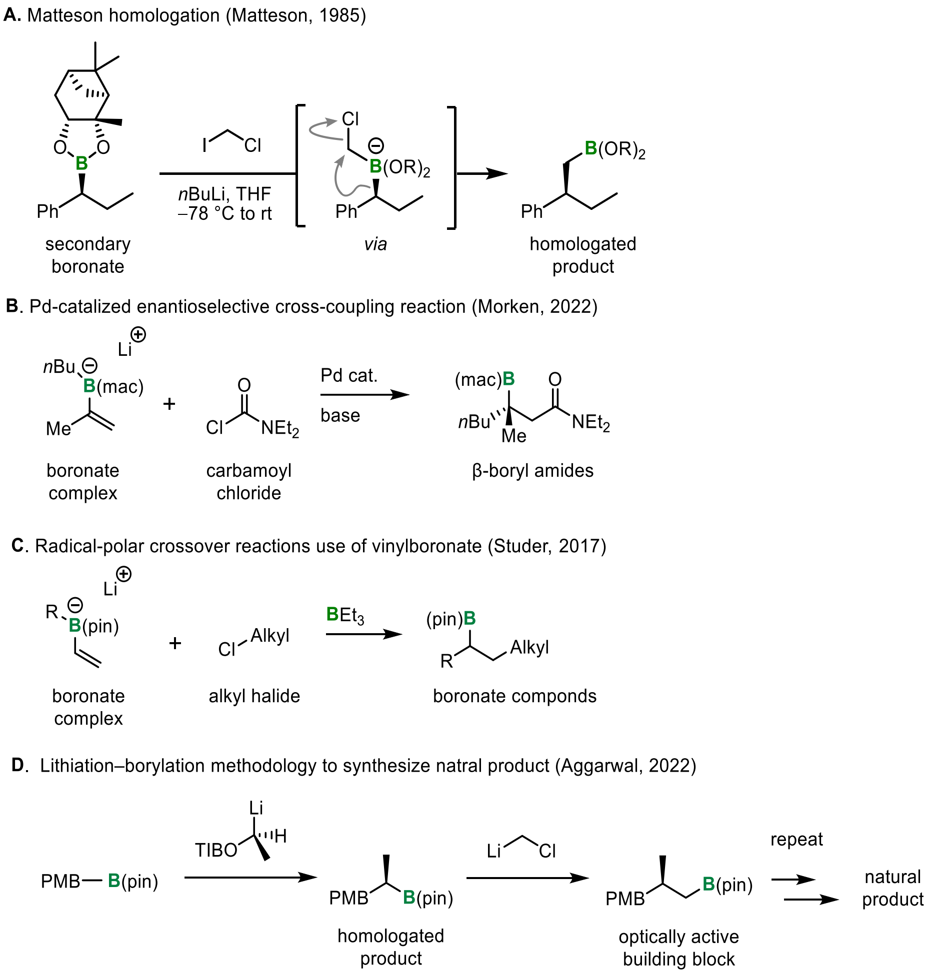


Figure 5. Selected recent works using boronate complexes.

In addition, the Aggarwal group reported fluorination via boronate complexes described below (Figure 6). In 2015, they developed the α-substitution reaction, optically active secondary boronic esters convert into optically active organofluorine compounds via S_E2_{inv} mechanism using Selectfluor®.[24] Moreover, they reported the useful strategy, providing access to an array of stereodefined tertiary and quaternary allylic products with allylic boronates and various electrophiles, e.g., amines, thiols, and Selectfluor®.[25]

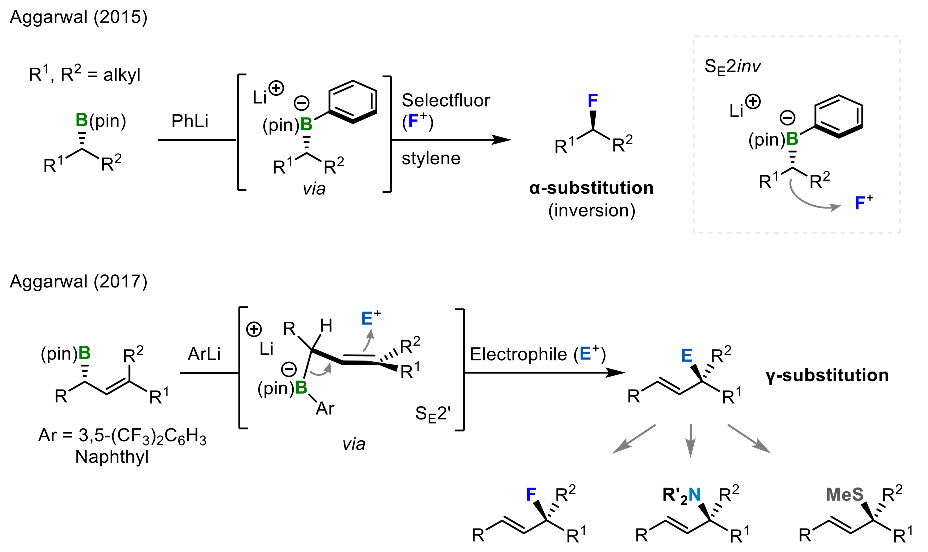


Figure 6. Fluorination reaction via boronate complexes

Only one case of synthesis of cyclopropane via boronate complexes has been reported by Fussain in 2014. The optically active boronic ester reacts with lithium reagents generated in situ and TCCA to afford the monochlorinated cyclopropane. They mentioned that the reaction proceeded via activation of alkene by TCCA and subsequent electrophilic cyclization (Figure 7). [26]

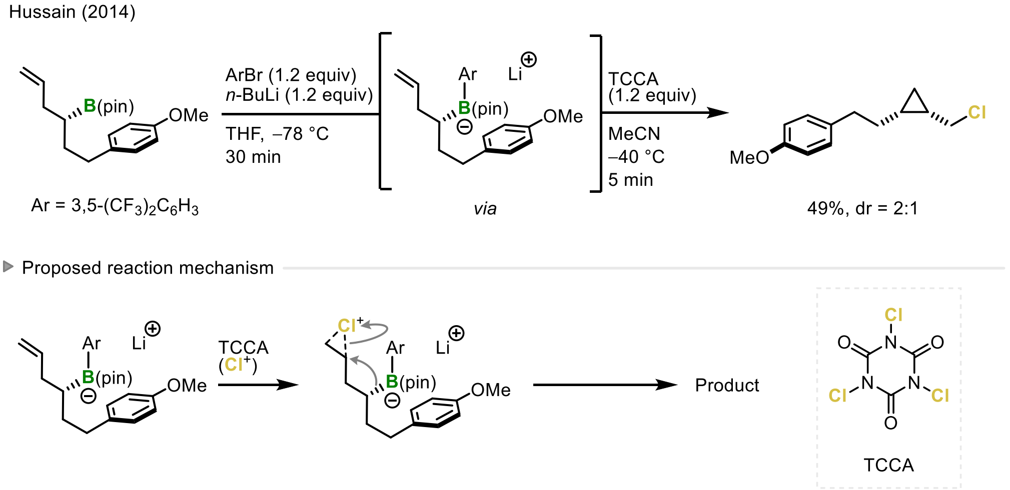
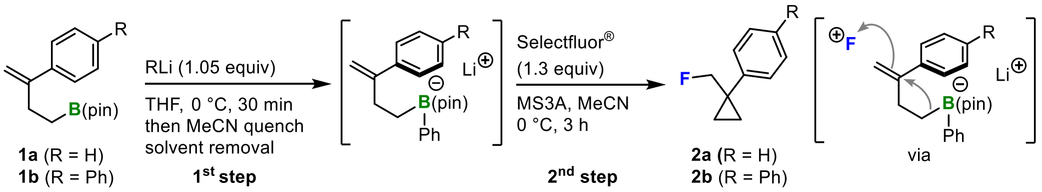


Figure 7. Construction of cyclopropane vial boronate complexes

3.2. Results and discussion

I started the development the reaction of *exo*-methylene homoallylic boronate using Selectfluor® as an electrophile and homoallylic boronate compound **1a** as model substrate under the standard condition described in Table 1. [15] First, the homoallylic boronate compound **1a** was treated with an organolithium reagent at 0 °C for 30 min and then quenched with acetonitrile. After solvent removal at room temperature, the mixture was dissolved by acetonitrile, and Selectfluor® was added at 0 °C. Fortunately, I obtained fluoromethylated product **2a** in 57% ^{19}F NMR yield using 1.05 equiv of PhLi at 0 °C (Table 1, entry 1). Homoallylic boronate compound, which has biphenyl moiety **1b** afforded **2b** in good yield under the same conditions as entry 1 (Table 1, entry 2, 77%). Furthermore, I investigated other lithium reagents, which were generated in situ by lithium/halogen exchange of the corresponding aryl bromides and *n*-butyllithium (*n*-BuLi), to tune the nucleophilicity of the boronate complex; the desired product was obtained in low or trace yields (Table 1, entries 3 and 4, 21% and trace).[27] *n*-BuLi was not acceptable for this system (Table 1, entry 5, trace). [27] The author revealed that the amount of PhLi (1.05 equiv) had a huge impact on the yield of the desired product (Table 1, entries 6–8, trace–50%). CH_2Cl_2 was not a suitable solvent during the formation of the boronate complex, resulting in a low yield (Table 1, entry 9, 15%). I tried to enhance the reaction by introducing 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in the second electrophilic cyclization step to stabilize the cationic boronate complex intermediate.[28] However, this resulted in a slight decrease in the yield (Table 1, entry 10, 49%). When the second step was conducted without removing the solvents after the first step, the yield of the desired product was decreased (Table 1, entry 11, 37%). Although I investigated the effect of other parameters, such as 1.1 equiv Selectfluor® and longer reaction time, the yield of the desired product slightly decreased (Table 1, entries 12 (51%) and 13 (52%)).

Table 1. Optimization of the reaction conditions[a]

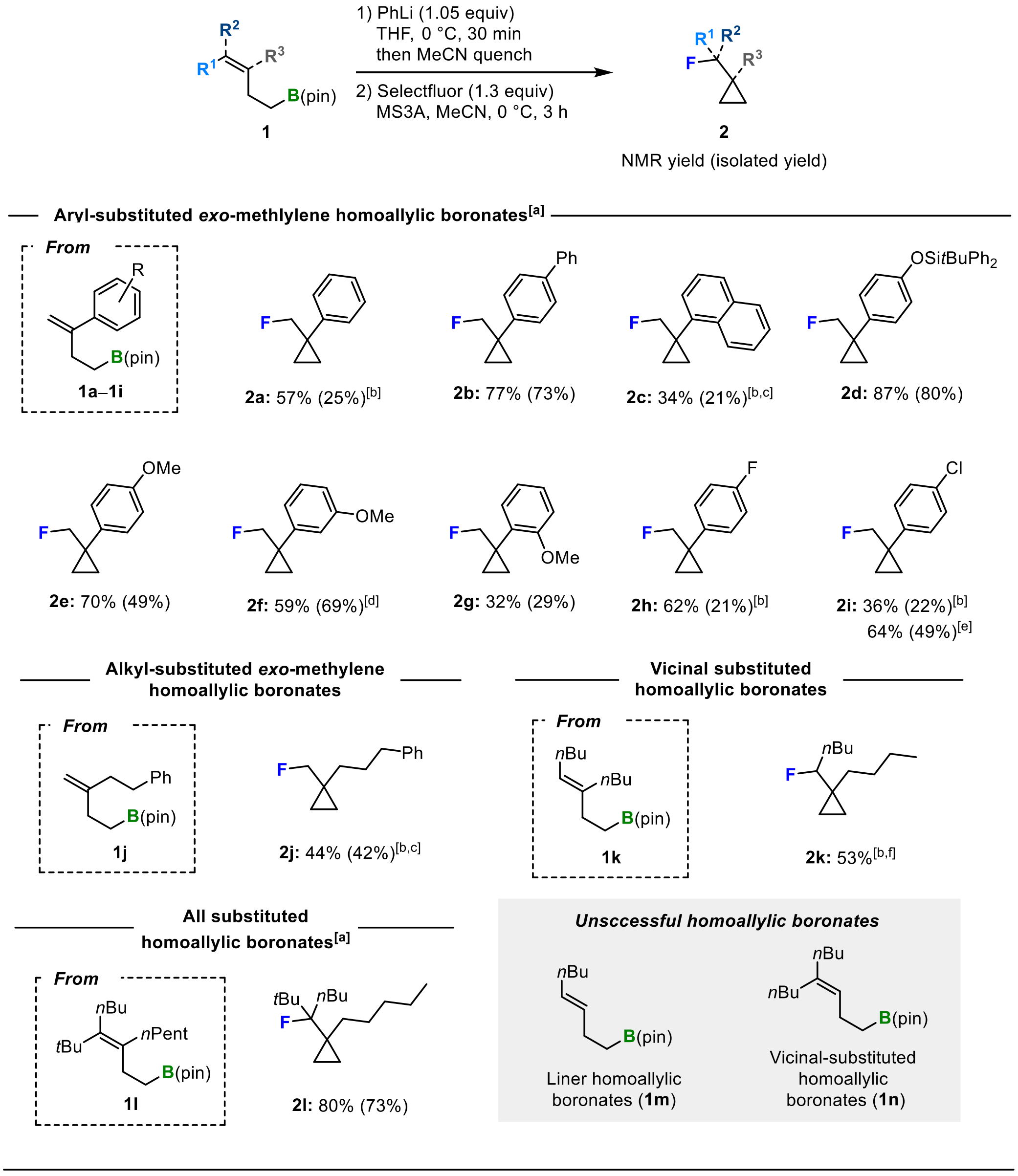


Entry	RLi	Deviation from the standard conditions	**2a** (%)[b]
1	PhLi	None	57 (25)[c]
2	PhLi	None	**2b** R = Ph : 77 (73) [c]
3	3,5-$(CF_3)_2C_6H_3Li$	0.95 equiv of lithium reagent was used	21
4	*p*-MeOC6H4Li	0.95 equiv of lithium reagent was used	Trace
5	*n*-BuLi	0.95 equiv of lithium reagent was used	Trace
6	PhLi	0.95 equiv of PhLi	50
7	PhLi	1.2 equiv of PhLi	35
8	PhLi	2.0 equiv of PhLi	Trace
9	PhLi	CH_2Cl_2 instead of THF	15
10	PhLi	HFIP:MeCN=1:1 instead of MeCN in 2nd step	49
11	PhLi	without solvent removal	37
12	PhLi	1.1 equiv of Selectfluor®	51
13	PhLi	Reaction time 6 h	52

[a]Reaction conditions: **1a** (0.2 mmol), 1.05 equiv of lithium reagent, and 1.3 equiv of Selectfluor®. The total solvent volume (0.05 M) was adjusted to 4 mL in the second step. [b]Determined by ^{19}F NMR analysis of the crude product with fluorobenzene as the internal standard. [c]Isolated yield.

Using the optimized reaction conditions, the author next explores the scope of homoallylic boronates (Table 2). The reaction of aryl-substituted *exo*-methylene substrates with simple aromatics such as phenyl, biphenyl, and naphthyl group afforded the desired products in moderate yields (**2a**–**2c**, 34–77%, details of X-ray analysis for **2b** are described in Supporting Information). Electron-donating groups, such as methoxy groups, and electron-withdrawing substituents, such as chloride and fluoride, were tolerated in this reaction and gave the desired products. The homoallylic boronates containing silyl ether (**1d**) and methyl ether (**1e**–**1g**) also could be applied to this reaction and afforded the desired products (**2d**–**2g**, 32–87%). The yield of products varied depending on the substitution position of the methoxy group (*p*-MeO: **2e**, 70%; *m*-MeO: **2f**; *o*-MeO: 59%; **2g**, 32%). Halogens on the aryl ring could also be employed (**2h**, 62%; **2i**, 36%). Alkyl-substituted *exo*-methylene homoallylic boronates afforded the desired cyclopropane ring (**2j**, 44%). 3,4-Disubstituted homoallylic boronate (**2k**) and 3,4,4-trisubstituted homoallylic boronate (**2l**) were also acceptable and gave the desired products in good yields (**2k**, 53%; **2l**, 80%). However, the monosubstituted (**1m**) and geminal-disubstituted (**1n**) homoallylic boronates did not afford the desired cyclopropane products. In many cases, the isolated yield of the products is low compared to their NMR yield. This is mainly due to the difficulty of removing a small amount of the by-products and the loss of evaporation during the purification step.

Table 2. Scope of homoallylic boronates[a]



[a]Reaction conditions: **1** (0.2 mmol), 1.05 equiv of organolithium reagent, and 1.3 equiv of Selectfluor®. The total solvent volume was adjusted to 4 mL (0.05 M) in the second step. Yields were determined using ^{19}F NMR analysis of the crude product with fluorobenzene as the internal standard. The isolated yields are shown in parentheses. [b]The reaction was conducted on a 0.4 mmol scale. [c]Containing small amounts of inseparable and unidentified impurities. [d]Containing a small amount of phenylboronic acid pinacol ester. [e]The reaction was conducted on a 1.0 mmol scale. [f]**2k** was detected by ^{19}F NMR and could not be isolated due to its instability during purification.

Next, I also conducted ^{11}B{^{1}H} NMR experiments to confirm the formation of the boronate complex intermediate (Figure 1). NMR experiment results showed that treating homoallylic boronate **1a** with 1.0 equiv of PhLi in CD_3CN-d_3 led to the formation of the corresponding boronate complex (δ 7.5 ppm). The cyclization resulted in the formation of cyclopropanation product **2a** by adding Selectfluor® to the boronate complex solution.

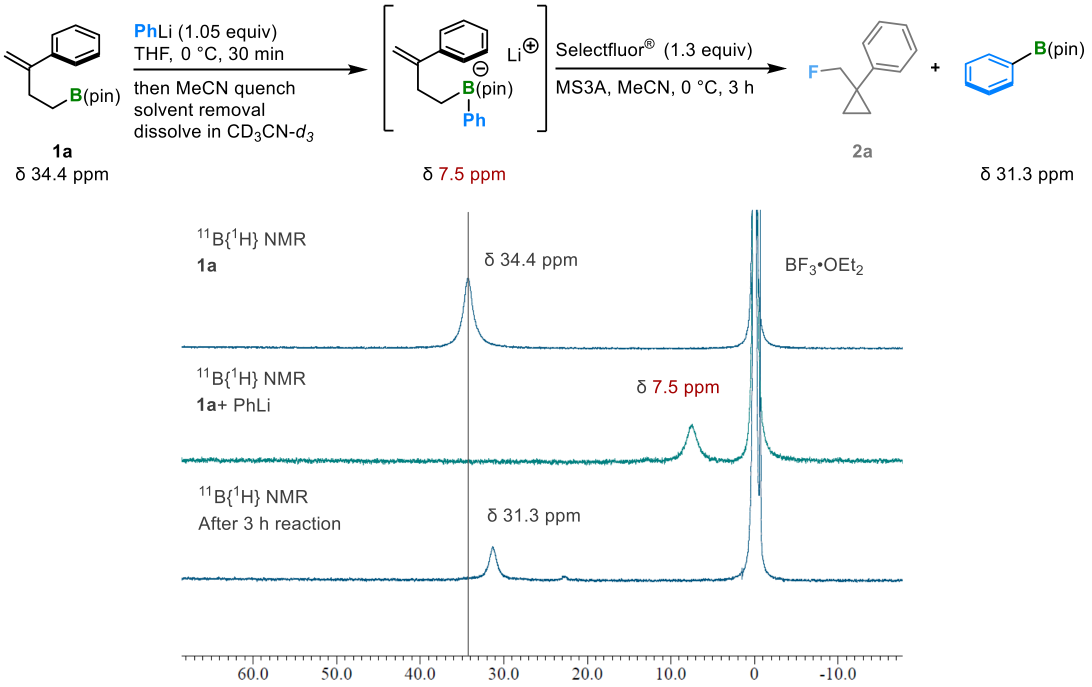


Figure 1. ^{11}B{^{1}H} NMR experiments

Finally, I carried out a further transformation to show the utility of this cyclization reaction for the synthesis of an important intermediate of fluoromethylated cyclopropane-containing bioactive compounds (Figure 2).[29] I could obtain the corresponding boronic acid (**3**) in 74% yield via a Pd-catalyzed borylation reaction.[30]

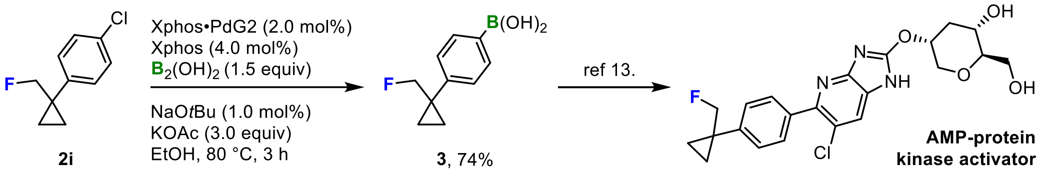


Figure 2. Application to the formal synthesis of a bioactive compound. The reaction was conducted on a 0.24 mmol scale

3.3. Conclusions

In summary, the author have developed the electrophilic cyclization via the boronate complex between various homoallylic boronates and Selectfluor® to access novel fluoromethylated cyclopropanes that were difficult to synthesize by using previous methods. This method could be applied to various substrates. Moreover, the intermediate boronate complex in this reaction was observed through ^{11}B NMR experiments. I also demonstrate the synthesis of a building block, including fluoromethyl-substituted cyclopropane for a bioactive compound. Following these results, I expected that the desired products can be used as new building blocks for introducing fluorine-containing cyclopropane motifs into synthetic targets or new intermediates.

3.4. Reference

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3.5. Experimental details

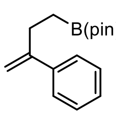
3.5.1. Instrumentation and Chemicals

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4A). NMR spectra were recorded on JEOL JNM-ECX400P, JNM-ECS400, JNM-ECA400, and JNM-ECB400 spectrometers (^{1}H: 400 MHz, ^{13}C: 100 MHz, ^{19}F: 373 MHz and ^{11}B: 128 MHz). Tetramethylsilane (^{1}H, δ 0.00), $CDCl_3$ (^{13}C, δ 77.0), and fluorobenzene (^{19}F, δ –113.60) were employed as the external standards, respectively. Fluorobenzene was used as an internal standard to determine ^{19}F NMR yield. $BF_3 \cdot Et_2O$ was used as an external standard for ^{11}B NMR analysis. Multiplicity was reported as follows: s = singlet, brs = broad, singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with a ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and an FID detector. Recycle preparative gel chromatography (GPC) was conducted with LaboACE LC-5060. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University. Single crystal X-ray structural analysis was performed on a Rigaku XtaLAB PRO MM007 diffractometer using graphite monochromated CuK_α radiation. The structure was solved by direct methods and expanded using Fourier techniques. Nonhydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. All calculations were performed using the Olex2 crystallographic software package except for refinement, which was performed using SHELXL.[1]

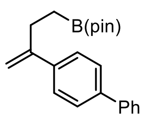
3.5.2. Substrate Preparation Procedure

The homoallylic boronates **1a**[2], **1b**[2], **1c**[2], **1e**[2], **1h**[3,] and **1i**[3] are known compounds and were prepared as described below. All spectroscopic data were matched in those reported. The new compounds **1d, 1f, 1g** were synthesized according to references and characterized as described below. The other homoallylic boronates **2j**[2] and **1l**[4] are known compounds and were prepared according to references and each general procedure. All spectroscopic data were matched in those reported. The new compound **1k** was synthesized and characterized, described below.

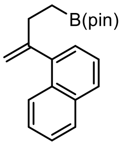
Table S1. Homoallylic boronates used in this study.



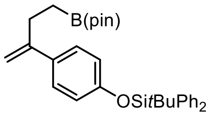
1a
(Procedure A or D)



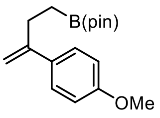
1b
(Procedure B)



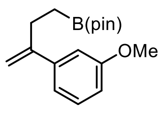
1c
(Procedure A)



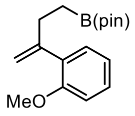
1d
(Procedure C)



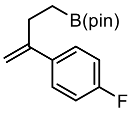
1e
(Procedure D)



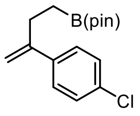
1f
(Procedure B)



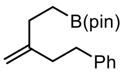
1g
(Procedure B)



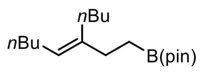
1h
(Procedure D)



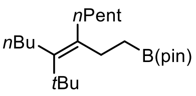
1i
(Procedure A or D)



1j
(Procedure A)

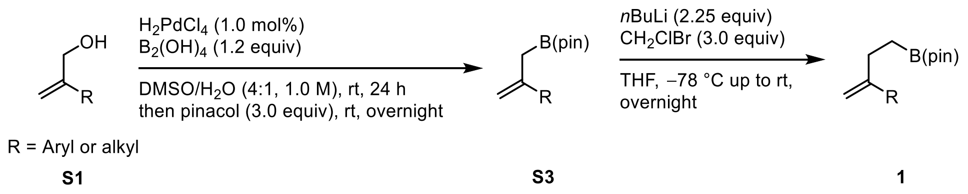


1k
(Procedure E)



1l
(Procedure F)

3.5.2.1. General Procedure of Aryl-substituted *exo*-methylene and alkyl-substituted *exo*-methylene synthesis (Procudure A).[5, 6, 7, 8]

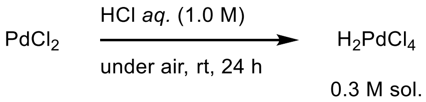


The corresponding aryl-substituted *exo*-methylene alcohol product **S1** was synthesized following previous reports.[5,6] The palladium(II)-catalyzed borylation of the corresponding allyl alcohols was performed following the literature conditions.[7] In a vial, a solution of dihydrogen tetrachloropalladate (II) (5.0 mol%) and tetrahydroxydiboron (1.2 equiv) was added to a solution of the corresponding allyl alcohol (1.0 equiv) in

DMSO/H_2O (4:1, 1.0 M) and the resulting mixture was stirred at room temperature for 24 h. After 24 h, pinacol (3.0 equiv) was added to the mixture, and the resulting mixture was stirred at room temperature for 3 h. After stirred, the reaction mixture was quenched by H_2O and extracted with hexane. The combined organic layer was then dried over Na_2SO_4. After filtration, the solvent was removed by rotary evaporator. Purified by silica gel column chromatography (typically, Et_2O/hexane 2:98–10:90) to obtain the corresponding aryl-substituted allylic boronate product **S3**.

The homologation reaction of **S3** was performed according to the literature procedure.[8] In an oven-dried reaction glassware, corresponding allylic boronate **S3** (1.0 equiv) and $BrCH_2Cl$ (3.0 equiv) were dissolved in THF (0.1 M) in a nitrogen atmosphere, and the mixture was cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 2.25 equiv) was then added dropwise to the reaction mixture, and the mixture was stirred at rt for overnight. The mixture was then quenched by the addition of H_2O and extracted three times with Et_2O. Next, the combined organic layer was washed with brine and dried over Na_2SO_4 followed by filtration. After evaporation, the crude material was purified by silica gel chromatography (Et_2O/hexane, 0:100–5:95) to give the corresponding homoallylic boronate product **1**.

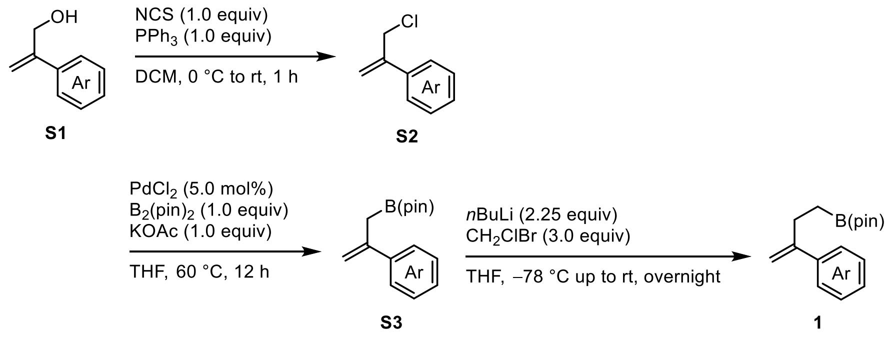
3.5.2.2. Preparation of dihydrogen tetrachloropalladate solution.[7]



$$PdCl_2 \xrightarrow[\text{under air, rt, 24 h}]{\text{HCl } aq. \text{ (1.0 M)}} \underset{\text{0.3 M sol.}}{H_2PdCl_4}$$

$PdCl_2$ (162 mg, 0.900 mmol) was weighed in a vial, and then aqueous HCl (1.0 M, 3.0 mL) was added. The vial was capped, and the mixture was stirred at room temperature for 24 h. The resulting aqueous H_2PdCl_4 solution (0.3 M) was stored under ambient conditions and used as such.

3.5.2.3. General Procedure of Aryl-substituted *exo*-methylene synthesis (Procedure B).[5, 6, 8, 9, 10]

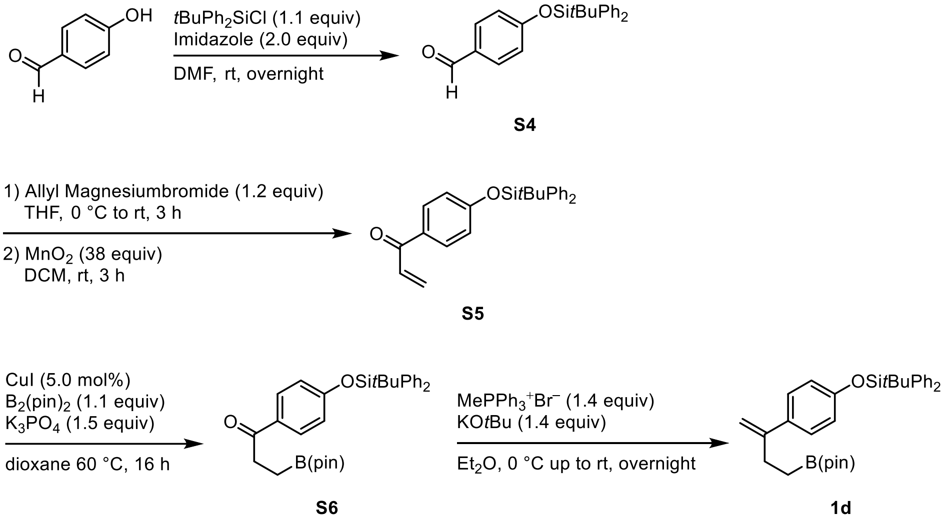


The corresponding aryl-substituted *exo*-methylene alcohol product **S1** was synthesized following previous reports.[5,9] The reaction was conducted following the literature.[6] In a vacuum-dried round-bottomed flask, the corresponding aryl-substituted *exo*-methylene alcohol product **S1** (1.0 equiv) and PPh_3 (1.1 equiv) were dissolved in dry CH_2Cl_2 (0.2 M) under the air and stirred for 10 min at 0°C. Then, NCS (1.1 equiv) was added to the mixture slowly and allowed to warm to room temperature, stirring for 1 h at the same temperature. After being stirred, the mixture was quenched by the addition of H_2O. And then, the mixture was extracted with CH_2Cl_2. The organic layer was dried over Mg_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography (typically, Et_2O/hexane 2:98–5:95) to obtain the corresponding aryl-substituted *exo*-methylene chloride product **S2**.

The palladium(II)-catalyzed borylation of the corresponding allyl chloride was performed following the literature conditions.[10] $PdCl_2$ (5.0 mol%), bis(pinacolato)diboron (1.0 equiv), and KOAc (1.0 equiv) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a Teflon®-coated rubber septum, it was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (1.0 M) was added to the vial through the rubber septum using a syringe. After stirring for 5 min, the corresponding chloride **S2** (1.0 equiv) was added to the mixture. The reaction mixture was stirred at 60 °C for 12 h. After stirring for 12 h, the mixture was directly filtered through a silica gel pad with Et_2O as an eluent. Then, the resultant solution was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (typically, Et_2O/hexane 2:98–10:90) to obtain the corresponding aryl-substituted allylic boronate product **S3**.

The homologation reaction of **S3** was performed according to the literature procedure.[8] In an oven-dried reaction glassware, corresponding allylic boronate **S2** (1.0 equiv) and $BrCH_2Cl$ (3.0 equiv) were dissolved in THF (0.1 M) in a nitrogen atmosphere, and the mixture was cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 2.25 equiv) was then added dropwise to the reaction mixture, and the mixture was stirred at rt overnight. The mixture was then quenched by the addition of H_2O and extracted three times with Et_2O. Next, the combined organic layer was washed with brine and dried over Na_2SO_4 followed by filtration. After evaporation, the crude material was purified by silica gel chromatography (Et_2O/hexane, 0:100–10:90) to give the corresponding homoallylic boronate product **1**.

3.5.2.4. Synthesis of *tert*-Butyldiphenyl(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-2-yl)phenoxy)silane (1d) (Procedure C).[11, 12, 13, 14]



The reaction was conducted following the literature.[11] In a vacuum-dried two-neck round-bottomed flask, 4-Hydroxybenzaldehyde (1.22 g, 10 mmol), Imidazole (1.37 g, 20 mmol, 2.0 equiv) was dissolved DMF (30 mL, 0.3 M) under a nitrogen atmosphere. *t*BuPh$_2$SiCl (2.85 mL, 11 mmol, 1.1 equiv) was added dropwise to the flask at room temperature and stirred overnight. The mixture was then quenched by the addition of H_2O and extracted three times with Et$_2$O. Next, the combined organic layer was washed with brine and dried over Mg_2SO_4 followed by filtration. After evaporation, the crude material was purified by silica gel chromatography (EtOAc/hexane, 2:98–10:90) to afford silyl-protected product **S4** (2.57 g, 7.12 mmol, 71%) as a colorless oil.

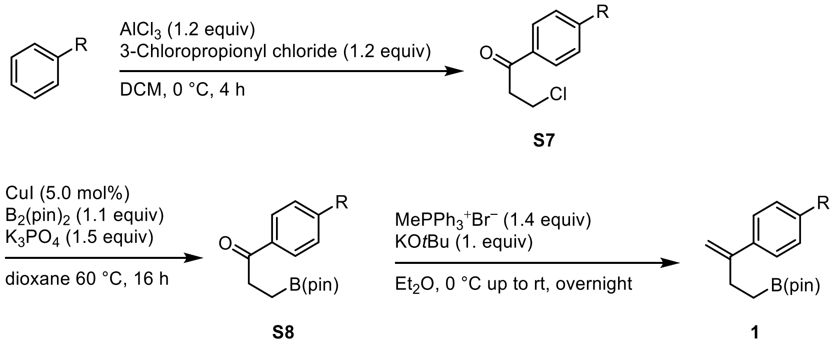
The reaction was conducted following the literature.[12] In a vacuum-dried two-neck round-bottomed flask, **S4** (1.2 g, 3.33 mmol) was dissolved THF (20 mL, 0.17 M) under a nitrogen atmosphere and allowed to cool to 0 ºC, stirred 10 min. Allyl magnesium bromide (1,0 M in THF, 4.0 mL, 3.99 mmol, 1.2 equiv) was added dropwise to the mixture at 0 ºC and stirred for 3 h. The mixture was then quenched by the addition of H_2O and extracted three times with Et$_2$O. Next, the combined organic layer was washed with brine, dried over $MgSO_4$, and followed by filtration. After evaporation, the crude material was used without purification. In a round-bottomed flask, the crude material was dissolved in DCM (60 mL). MnO_2 (11 g, 126 mmol, 38 equiv) was added to the mixture under the air and stirred at room temperature for 3 h. After being stirred for 3 h, the mixture was followed by filtration and evaporation. The residue was purified by silica gel chromatography (EtOAc/hexane, 5:95–20:80) to afford enone product **S5** (877.9 mg, 2.27 mmol, 86%) as a light pale yellow oil.

The reaction was performed in a modified procedure according to the literature.[13] Bis(pinacolato)diboron (614.5 mg, 2.4 mmol, 1.1 equiv), CuI (21 mg, 0.11 mmol, 0.05 equiv), and K_3PO_4 (700 mg, 3.3 mmol, 1.5 equiv) were placed in a vacuum dried two-neck round-bottomed flask. The flask was connected to a vacuum/nitrogen manifold, evacuated and then backfilled with nitrogen. 1,4-dioxane (10 mL) was added to the mixture and stirred for 30 min at room temperature. After being stirred, enone product **S5** (750 mg, 1.94 mmol, 1.0 equiv) was added to the mixture and allowed to heat to 60 ºC, stirred for 20 h. After the reaction was completed, the reaction mixture was filtered and evaporated. The residue was purified by silica gel chromatography (EtOAc/hexane, 2:98–20:80) to afford borylated product **S6** (572.5 mg, 1.1 mmol, 55%) as a colorless oil.

The reaction was performed in a modified procedure according to the literature.[14] KO*t*Bu (175.2 mg, 1.56 mmol, 1.4 equiv) and $MePh_3P^+Br^-$ (556.4 mg, 1.56 mmol, 1.4 equiv) were placed in a vacuum-dried two-neck round-bottomed flask. The flask was connected to a vacuum/nitrogen manifold and evacuated and then backfilled with nitrogen. Et_2O (4 mL) was added to the mixture and stirred for 1 h at room temperature. After being stirred, borylated product **S6** (572.5 mg, 1.1 mmol, 1.0 equiv) in Et_2O (1 mL) was added to the mixture at 0 ºC and allowed to warm to room temperature. After stirred overnight, the mixture was filtered and evaporated. The residue was purified by silica gel chromatography (Et_2O/hexane, 0:100–6:94) to afford homoallylic boronate **1d** (66.2 mg, 0.13 mmol, 12%) as a colorless oil.

^{1}H NMR (396 MHz, $CDCl_3$): δ 0.89–0.98 (m, 2H), 1.09 (s, 9H), 1.22 (s, 12H), 2.50 (t, *J* = 7.6 Hz, 2H), 4.93 (s, 1H), 5.12 (s, 1H), 6.69 (dd, *J* = 1.6, 8.6 Hz, 2H), 7.16 (dd, *J* = 1.2, 8.6 Hz, 2H), 7.33–7.46 (m, 6H), 7.71 (dt, *J* = 1.4, 4.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4 (*C*), 24.8 (*C*H_3), 26.5 (*C*H_3), 29.1 (*C*H_2), 83.0 (*C*), 109.3 (*C*H_2), 119.2 (*C*H), 126.8 (*C*H), 127.7 (*C*H), 129.8 (*C*H), 133.0 (*C*), 134.1 (*C*), 135.5 (*C*H), 149.5 (*C*), 154.9 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{32}H_{41}BO_3Si$, 511.2954; found, 511.2948.

3.5.2.5. General Procedure of Aryl-substituted *exo*-methylene synthesis (Procedure D).[13, 14, 15]

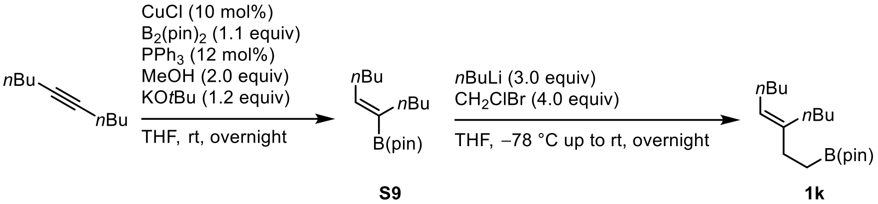


The reaction was performed modified procedure according to the literature.[15] $AlCl_3$ (1.2 equiv) wase placed in a vacuum dried two-neck round-bottomed flask. DCM (0.75 M) was added to the mixture under a nitrogen atmosphere and stirred for 10 min at 0 ºC. After being stirred, the corresponding aromatic (1.0 equiv) was added to the mixture. 3-chloropropionyl chloride was added to the mixture at 0 ºC and allowed to warm to room temperature and stirred for overnight. After the reaction was completed, the reaction mixture was quenched by addition of H_2O and extracted DCM, dried over $MgSO_4$ and followed by filtration. After evaporation, the crude material was purified by silica gel chromatography (only hexane) to afford ketone product **S7**.

The reaction was performed in a modified procedure according to the literature.[13] Bis(pinacolato)diboron (1.1 equiv), CuI (0.05 equiv), and K_3PO_4 (1.5 equiv) were placed in a vacuum-dried two-neck round-bottomed flask. The flask was connected to a vacuum/nitrogen manifold and, evacuated and then backfilled with nitrogen. 1,4-Dioxane (0.2 M) was added to the mixture and stirred for 30 min at room temperature. After being stirred, ketone **S7** (1.0 equiv) was added to the mixture and allowed to heat to 60 ºC, stirred for 20 h. After the reaction was completed, the reaction mixture was filtered and evaporated. The residue was purified by silica gel chromatography (typically, EtOAc/hexane, 2:98–20:80) to afford borylated product **S8**.

The reaction was performed in a modified procedure according to the literature.[14] KO*t*Bu (1.4 equiv) and $MePh_3P^+Br^-$ (1.4 equiv) were placed in a vacuum-dried two-neck round-bottomed flask. The flask was connected to a vacuum/nitrogen manifold and evacuated and then backfilled with nitrogen. Et_2O (total Et_2O 0.25 M) was added to the mixture and stirred for 1 h at room temperature. After being stirred, borylated product **S8** in Et_2O (total Et_2O 0.25 M) was added to the mixture at 0 ºC and allowed to warm to room temperature. After stirred overnight, the mixture was filtered and evaporated. The residue was purified by silica gel chromatography (Et_2O/hexane, 0:100–6:94) to afford homoallylic boronate **1.**

3.5.2.6. Synthesis of 1k (Procedure E).[16]



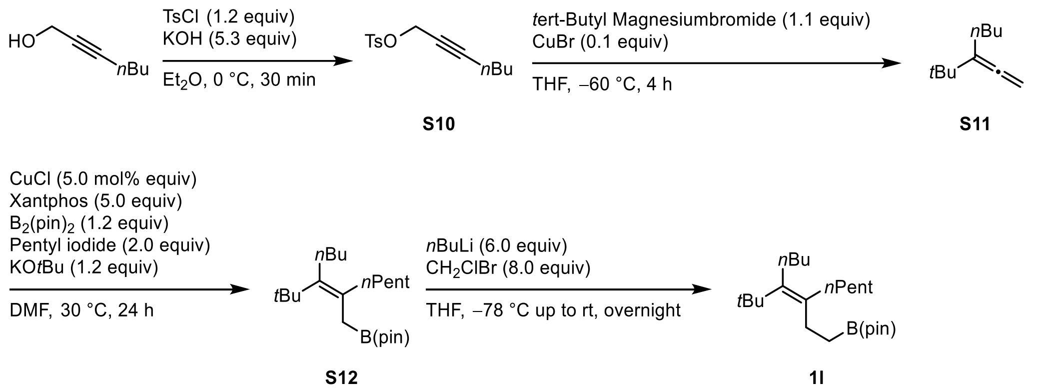
The reaction was performed modified procedure according to the literature.[16] In a vacuum-dried two-neck round-bottomed flask, An oven-dried reaction vial was charged with copper chloride (149.6 g, 0.05 mol), bis(pinacolato)diboron (1.39 g, 5.5 mmol, 1.1 equiv), PPh_3 (157.4 mg, 0.6 mmol) and transferred to an argon-filled glove box. After KO*t*Bu (480.5 mg, 6.0 mmol, 1.2 equiv) was added to the flask, it was capped with a rubber septum and removed from the glove box. The solids were suspended in THF (44 mL) and added MeOH (319.8 mg, 10 mmol, 2.0 equiv), and the suspension was allowed to stir for 10 min at room temperature. 5-hexyne (691.3 mg, 10 mmol, 1.0 equiv) was added to the suspension, and the mixture was stirred at room temperature overnight. After being stirred, the mixture was passed through a short plug of silica gel, and eluted with Et_2O. The resulting oily residue was subjected to silica gel chromatography (Et_2O/hexane, typically 0:100–4:96) to give borylation product **S9** as a colorless oil.

The homologation reaction of **S9** was performed according to the literature procedure.[8] In an oven-dried reaction glassware, vinyl boronate **S9** (706.2 mg, 2.2 mmol, 1.0 equiv) and $BrCH_2Cl$ (0.59 mL, 8.8 mmol, 4.0 equiv) were dissolved in THF (0.1 M) in a nitrogen atmosphere, and the mixture was cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 6.6 mmol, 4.13 mL, 3.0 equiv) was then added dropwise to the reaction mixture, and the mixture was stirred at room temperature overnight. The mixture was then quenched by the addition of H_2O and extracted three times with Et_2O. Next, the combined organic layer was washed with brine and dried over Na_2SO_4 followed by filtration. After evaporation, the crude material was purified by silica gel chromatography (Et_2O/hexane, 0:100–10:90), further purified by GPC to give the homoallylic boronate product **1k** as a colorless oil (118.7 mg, mmol, 18%)

^1H NMR (396 MHz, $CDCl_3$): δ 0.83–0.93 (m, 8H), 1.23 (s, 12H), 1.26–1.39 (m, 8H), 1.92–2.03 (m, 4H), 2.09 (t, *J* = 7.9 Hz, 2H), 5.10 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 14.1 (CH_3), 22.4 (CH_2), 22.9 (CH_2), 24.8 (CH_3), 27.3 (CH_2), 29.99 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 32.4 (CH_2), 82.8 (C), 123.3

(*C*H), 141.0 (*C*). HRMS–ES (m/z): $[M]^+$ calcd for $C_{18}H_{35}BO_2$, 293.2766; found, 293.2758.

3.5.2.7. Synthesis of 1l (Procedure F).[4]



All reaction was performed procedure according to the literature.[4] KOH (11 g, 196 mmol, 5.3 equiv) was placed in a vacuum-dried two-neck round-bottomed flask. The flask was connected to a vacuum/nitrogen manifold and evacuated and then backfilled with nitrogen. Et_2O (60 mL) and 2-Heptyn-1-ol (4.18 g, 37 mmol, 1.0 equiv) were added to the flask. The mixture was allowed to 0 ºC. TsCl (8.46 g, 44 mmol, 1.2 equiv) was added at a small portion to the flask at 0 ºC and stirred for 30 min. After being stirred, the mixture was quenched by ice H_2O, extracted Et_2O, and dried over $MgSO_4$ followed by filtration. After evaporation, the crude material was used in the next step without any purification.

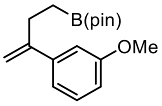
CuBr (531 mg, 3.7 mmol, 0.1 equiv) was placed in a vacuum-dried two-neck round-bottomed flask. The flask was connected to a vacuum/nitrogen manifold and, evacuated and then backfilled with nitrogen. THF (60 mL) and tosylated-product **S10** (w/o purification material, c.a. 37 mmol, 1.0 equiv) were added to the flask subsequently. The mixture was allowed to –60 ºC and stirred for 30 min. *tert*-butyl magnesium chloride (20.4 mL, 40.7 mmol, 1.1 equiv) was added dropwise with a syringe pump over 1 h and stirred at –60 ºC, stirred for 4 h. After being stirred, the mixture was allowed to warm to 0 ºC and quenched carefully by addition of NH_4Cl *aq*. The mixture was extracted by Et_2O and dried over $MgSO_4$ followed by filtration. After evaporation, the oily crude material was purified by silica gel chromatography (Et_2O/hexane, 0:100–20:80) to afford allene product **S11** (3.14 g, 20.6 mmol, 56%) as a colorless oil.

CuCl (15 mg, 0.15 mmol), Xantphos (87mg, 0.15 mmol), bis(pinacolato)diboron (914.4mg, 3.6 mmol), and KO*t*Bu (406.2 mg, 3.6 mmol) were placed in an oven-dried flask in an argon-filled glove box. After the flask was taken from the glove box, dry DMF (6.0 mL) was added to the vial through the rubber septum using a syringe. After stirring for 10 min, allene product **S11** (0.50 mmol) and pentyl iodide (1.19 g, 1.0 mmol) were added to the mixture. The reaction mixture was stirred at 30 °C for 24 h. After the reaction was completed, the reaction mixture was passed through a short silica gel column eluting with Et_2O. The crude material was purified by flash column chromatography (SiO_2, Et_2O/hexane, 0:100–3:97) to give the allyl boronate **S12**.

Homologation reaction of **S12** was performed according to the literature procedure.[8] In an oven-dried reaction glassware, **S12** (600 mg, 1.7 mmol, 1.0 equiv) and $BrCH_2Cl$ (0.96 mL, 13.7 mmol, 8.0 equiv) were dissolved in THF (0.1 M) in a nitrogen atmosphere, and the mixture was cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 10.3 mmol, 6.78 mL, 6.0 equiv) was then added dropwise to the reaction mixture, and the mixture was stirred at room temperature for overnight. The mixture was then quenched by the addition of H_2O and extracted three times with Et_2O. Next, the combined organic layer was washed with brine and dried over Na_2SO_4 followed by filtration. After evaporation, the crude material was purified by silica gel chromatography (Et_2O/hexane, 0:100–10:90), further purified by GPC to give the homoallylic boronate product **1l** as a colorless oil (66.8 mg, 0.11 mmol, 11%). All spectrums were matched to the previous report.[4]

3.6. Substrate Characterization

2-(3-(3-Methoxyphenyl)but-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1f).

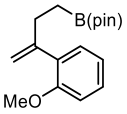


1f

The reaction was conducted with 472 mg (0.20 mmol) of ketone following Procedure A. Product **1f** was purified by silica gel chromatography (silica gel, Et_2O/hexane, 0:100–6:94), further purified by GPC and obtained in 28% yield (140.9 mg, 0.28 mmol, colorless oil).

^{1}H NMR (396 MHz, $CDCl_3$): δ 0.99 (t, J = 7.9 Hz, 2H), 1.24 (s, 12H), 2.59 (t, J = 7.9 Hz, 2H), 3.82 (s, 3H), 5.07 (s, 1H), 5.24 (s, 1H), 6.90 (dd, J = 0.48, 7.3 Hz, 1H), 6.95 (s, 1H), 7.01 (d, J = 7.5 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.8 (br, B–*C*H), 24.8 (*C*H_3), 29.4 (*C*H_2), 55.2 (*C*H_3), 83.0 (*C*), 111.2 (*C*H_2), 112.1 (*C*H), 112.4 (*C*H), 118.8 (*C*H), 129.1 (*C*H), 143.3 (*C*), 150.2 (*C*), 159.4 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{17}H_{25}BO_3$, 287.1933; found, 287.1927.

2-(3-(3-Methoxyphenyl)but-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2g).



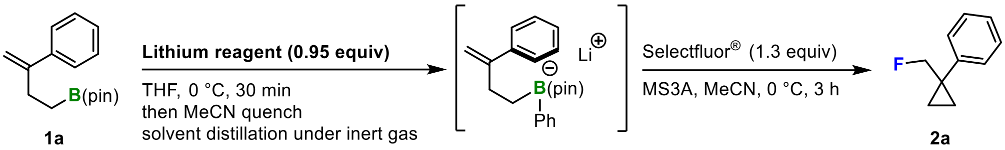
1g

The reaction was conducted with 645.4 mg (2.34 mmol) of ketone following Procedure A. Product **2g** was purified by silica gel chromatography (silica gel, EtOAc/hexane, 0:100–5:95), further purified by GPC and obtained in 19% yield (130.1 mg, 0.19 mmol, colorless oil).

^{1}H NMR (396 MHz, $CDCl_3$): δ 0.89 (t, J = 7.9 Hz, 2H), 1.23 (s, 12H), 2.55 (t, J = 8.1 Hz, 2H), 3.80 (s, 3H), 4.95 (s, 1H), 5.15 (s, 1H), 6.87 (dt, J = 7.3, 14.5 Hz, 2H), 7.11 (dt, J = 1.4, 4.7 Hz, 1H), 7.19–7.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8 (*C*H_3), 30.5 (*C*H_2), 55.4 (*C*H_3), 82.9 (*C*), 110.5 (*C*H), 112.7 (*C*H_2), 120.3 (*C*H), 128.1 (*C*H), 130.2 (*C*H), 132.4 (*C*), 150.7 (*C*), 156.4 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{17}H_{25}BO_3$, 287.1933; found, 287.1927.

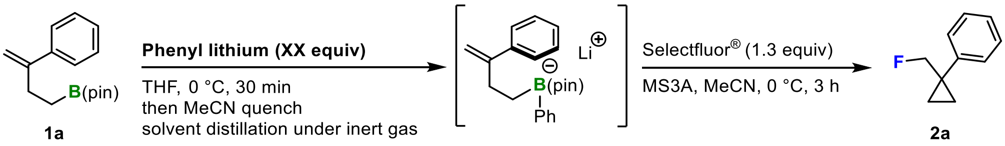
3.7. Optimizations[a]

3.7.1. Screening of lithium reagent



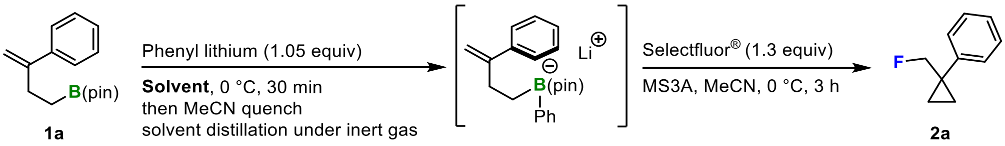
Entry	Lithium reagent	^{19}F NMR yield of **2a** (%)
1	Phenyl lithium	50
2	3,5-$(CF_3)_2C_6H_3Li$	21
3	*p*-$MeOC_6H_4Li$	N.D.
4	*n*-BuLi	Trace

3.7.2. Screening of equivalent of phenyl lithium



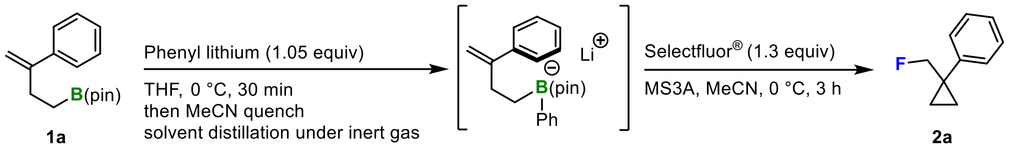
Entry	Equivalent	^{19}F NMR yield of **2a** (%)
1	0.95	50
2	1.05	57
3	1.2	35
4	2.0	Trace

3.7.3. Screening of Solvent



Entry	Solvent	^{19}F NMR yield of **2a** (%)
1	THF	50
2	Et_2O	21
3	DCM	N.D.
4	No distillation	Trace

3.7.4. Screening of other factors



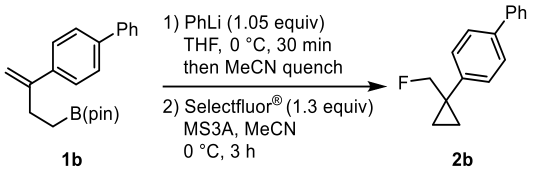
Entry	Deviation from condition	^{19}F NMR yield of **2a** (%)
1	1.1 equiv of Selectfluor®	51
2	1 h rection time instead of 3 h	51
3	6 h rection time instead of 3 h	52
4	HFIP : MeCN = 1 : 1 instead of only MeCN	49

[a] Reaction was conducted in 0.2 mmol scale.

3.8. General Experimental Procedure

Attention: All cyclopropane compounds are fragile under acidic conditions (even acidic atmosphere).

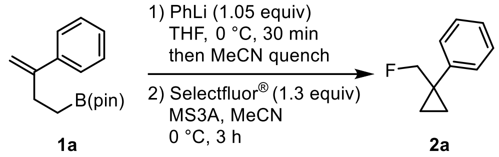
3.8.1. Procedure for the cyclopropanation for 4-[1-(fluoromethyl)cyclopropyl]-1,1'-biphenyl (2b) (0.2 mmol scale).



Homoallylic boronate **1b** (66.7 mg, 0.2 mmol) was placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a Teflon®-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (2 mL) was added to the vial through the rubber septum using a syringe and allowed to cool to 0 °C and stirred for 10 minutes. After stirring for 10 minutes, Phenyl lithium (116 µL, 1.05 equiv) was added to the mixture. The reaction mixture was stirred at 0 °C for 30 min. After stirring for 30 min, the mixture was quenched by MeCN (400 µL) at 0 °C and stirred at room temperature for 10 min. After stirring for 10 min at room temperature, the solvent (THF) was then removed in vacuo and the crude dissolved in dry MeCN (2.0 mL) and allowed to cool to 0 °C, stirred 10 min at the same temperature. Another oven-dried reaction vial was charged with MS 3A (80 mg) and dried up with a heat gun in vacuo. After Selectfluor® (92.3 mg, 1.3 equiv) was placed, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry MeCN (1.4 mL) was added to the vial through the rubber septum using a syringe and allowed to cool to 0 °C and stirred for 10 min. The boronate complex solution (2.0 mL in MeCN) was added to the vial containing Selecfluor® solution dropwise at 0 °C and stirred at 0 °C for 3 h. After being stirred for 3 h, the reaction mixture was passed through a short silica gel column (Φ: 10 mm, the height of the silica-gel column: 30 mm), eluting with Et_2O. The solvents were removed using a rotary evaporator with an ice bath. (The product is volatile under pressure.) The crude material was purified by flash column chromatography (SiO_2, Et_2O/hexane, 0:100–4:96) and further purified by GPC to give the **2b** as a white solid (33.1 mg, 0.146 mmol, 73%).

^{1}H NMR (401 MHz, $CDCl_3$): δ 0.96–1.09 (m, 4H), 4.48 (d, *J* = 48.9 Hz, 2H), 7.30–7.38 (m, 1H), 7.39–7.47 (m, 4H). 7.51–7.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.78 ($\mathit{C}H_2$), 11.85 ($\mathit{C}H_2$), 25.5 (d, *J* = 22.0 Hz, *C*), 90.5 (d, *J* = 172.5 Hz, $\mathit{C}H_2$), 127.0 (*C*H), 127.1 (*C*H), 127.2 (*C*H), 128.7 (*C*H), 128.9 (*C*H), 139.6 (*C*), 140.8 (*C*), 141.0 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –210.6 (t, *J* = 136.5 Hz, 1F). HRMS–EI (m/z): [M]+ calcd for $C_{16}H_{15}F$, 226.1158; found, 226.1152.

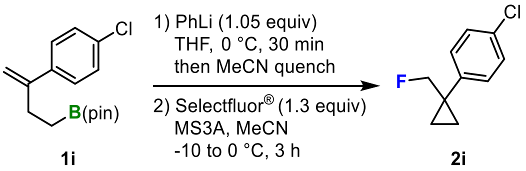
3.8.2. Procedure for the cyclopropanation for [1-(fluoromethyl)cyclopropyl]benzene (2a) (0.4 mmol scale).



Homoallylic boronate **1a** (103.1 mg, 0.4 mmol) was placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a Teflon®-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (4 mL) was added to the vial through the rubber septum using a syringe and allowed to cool to 0 °C and stirred for 10 minutes. After stirring for 10 minutes, phenyl lithium (230 µL, 1.05 equiv) was added to the mixture. The reaction mixture was stirred at 0 °C for 30 min. After stirring for 30 min, the mixture was quenched by MeCN (800 µL) at 0 °C and stirred at room temperature for 10 min. After stirring for 10 min at room temperature, the solvent (THF) was then removed in vacuo and the crude dissolved in dry MeCN (4.0 mL) and allowed to cool to 0 °C, stirred 10 min at the same temperature. Another oven-dried reaction vial was charged with MS 3A (160 mg) and dried up with a heat gun in vacuo. After Selectfluor® (184.2 mg, 1.3 equiv) was placed, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry MeCN (2.8 mL) was added to the vial through the rubber septum using a syringe and allowed to cool to 0 °C and stirred for 10 min. The boronate complex solution (4.0 mL in MeCN) was added to the vial containing Selecfluor® solution dropwise at 0 °C and stirred at 0 °C for 3 h. After being stirred for 3 h, the reaction mixture was passed through a short silica gel column (Φ: 10 mm, the height of the silica-gel column: 30 mm), eluting with Et_2O. The solvents were removed using a rotary evaporator with an ice bath. (The product is volatile under pressure.) The crude material was purified by flash column chromatography (SiO_2, Et_2O/pentane, 0:100–4:96) and further purified by GPC to give the **2a** as a colorless oil (15.2 mg, 0.10 mmol, 25%).

^{1}H NMR (401 MHz, $CDCl_3$): δ 0.82–1.06 (m, 4H), 4.44 (d, *J* = 48.5 Hz, 2H), 7.17–7.27 (m, 2H), 7.28–7.39 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.59 (*C*H_2), 11.66 (*C*H_2), 25.8 (d, *J* = 22.0 Hz, *C*), 90.5 (d, *J* = 172.5 Hz, *C*H_2), 126.7 (*C*H), 128.3 (*C*H), 128.6 (*C*H), 141.9 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –211.2 (t, *J* = 43.4 Hz, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{10}H_{11}F$, 150.0845; found, 150.0841.

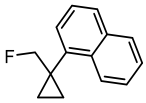
3.8.3. Procedure for the cyclopropanation of 1i (1.0 mmol scale)



Homoallylic boronate **1i** (292.6 mg, 1.0 mmol) was placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a Teflon®-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (10 mL) was added to the vial through the rubber septum using a syringe and allowed to cool to 0 ℃ and stirred for 10 minutes. After stirring for 10 minutes, Phenyl lithium (580 μL, 1.05 equiv) was added to the mixture. The reaction mixture was stirred at 0 °C for 30 min. After stirring for 30 min, the mixture was stirred at room temperature for 10 min. After stirring for 10 min at room temperature, the solvent (THF) was then removed in vacuo and the crude dissolved in dry MeCN (10 mL) and allowed to cool to –10 ℃, stirred 10 min at the same temperature. Another oven-dried reaction vial was charged with MS 3A (400 mg) and dried up with a heat gun in vacuo. After Selectfluor® (460.5 mg, 1.3 equiv) was placed, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry MeCN (9 mL) was added to the vial through the rubber septum using a syringe and allowed to cool to –10 ℃ and stirred for 10 min. The boronate complex solution (10 mL in MeCN) was added to the vial containing Selecfluor® solution slowly dropwise at –10 ℃ and allowed to warm to 0 ℃ gradually, then stirred at 0 ℃ for 3 h. After being stirred for 3 h, the reaction mixture was passed through a short silica gel column (Φ: 10 mm, the height of the silica-gel column: 30 mm), eluting with Et_2O. The solvents were removed using a rotary evaporator with an ice bath. (The product is volatile under the pressure.) The crude material was purified by flash column chromatography (SiO_2, Et_2O/pentane, 0:100–4:96) and further purified by GPC to give the cyclopropane product **2i** as a colorless oil (89.78 mg, 0.49 mmol, 49%).

3.9. Characterization of Products

1-[1-(Fluoromethyl)cyclopropyl]naphthalene (2c)

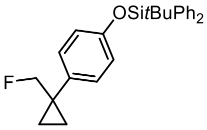


2c

The reaction was conducted with 123.1 mg (0.40 mmol) of **1c**. Product **2c** was purified by silica gel chromatography (silica gel, Et_2O/pentane, 0:100–4:96), further purified by GPC, and obtained in 21% yield (15.2 mg, 0.10 mmol, colorless oil).

^1H NMR (396 MHz, $CDCl_3$): δ 1.04–1.12 (m, 2H), 1.17–1.24 (m, 2H), 4.54 (d, *J* = 48.3 Hz, 2H), 7.37–7.64 (m, 4H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 8.33 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.26 (CH_2), 11.33 (CH_2), 24.7 (d, *J* = 23.0 Hz, *C*), 90.3 (d, *J* = 173.4 Hz, CH_2), 124.4 (*C*H), 125.4 (*C*H), 125.5 (*C*H), 125.9 (*C*H), 127.9 (*C*H), 128.8 (d, *J* = 4.8 Hz, *C*H), 132.5 (*C*), 133.9 (*C*), 137.5 (*C*). ^{19}F NMR (373 MHz, $CDCl_3$): δ –210.5 (t, *J* = 52.0 Hz, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{14}H_{13}F$, 200.1001; found, 200.0998.

Tert-butyl{4-[1-(fluoromethyl)cyclopropyl]phenoxy}diphenylsilane (2d)

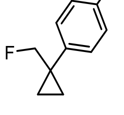


2d

The reaction was conducted with 102.5 mg (0.20 mmol) of **1d**. Product **2d** was purified by silica gel chromatography (silica gel, Et_2O/hexane, 0:100–2:98), further purified by GPC, and obtained in 80% yield (64.6 mg, 0.16 mmol, colorless oil).

^1H NMR (392 MHz, $CDCl_3$): δ 0.86 (s, 4H), 1.08 (s, 9H), 4.34 (d, *J* = 48.7 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.33–7.46 (m, 6H), 7.71 (d, *J* = 6.7 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.37 (CH_2), 11.43 (CH_2), 25.1 (d, *J* = 22.1 Hz, *C*), 90.7 (d, *J* = 168.4 Hz, CH_2), 119.3 (*C*H), 127.7 (*C*H), 129.4 (*C*H), 129.8 (*C*H), 132.9 (*C*), 134.2 (*C*), 135.5 (*C*H), 154.2 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –211.2 (t, *J* = 52 Hz, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{26}H_{29}FOSi$, 404.1972; found, 404.1969.

1-[1-(Fluoromethyl)cyclopropyl]-4-methoxybenzene (2e)

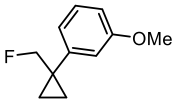


2e

The reaction was conducted with 57.8 mg (0.20 mmol) of **1e**. Product 2**e** was purified by silica gel chromatography (silica gel, Et_2O/pentane, 0:100–4:96), obtained in 49% yield (17.7 mg, 0.098 mmol, colorless oil).

^{1}H NMR (392 MHz, $CDCl_3$ (through Al_2O_3): δ 0.88–0.95 (m, 4H), 3.79 (s, 3H), 4.38 (d, *J* = 48.7 Hz, 2H), 6.80–6.89 (m, 2H), 7.23–7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.2 (*C*H_2), 11.3 (*C*H_2), 25.3 (d, *J* = 23.0 Hz, *C*), 55.3 (*C*H_3), 90.8 (d, *J* = 172.4 Hz, *C*H_2), 113.7 (*C*H), 130.0 (*C*H), 134.0 (*C*), 158.4 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –211.2 – –210.8 (m, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{11}H_{13}FO$, 180.0950; found, 180.0949.

1-[1-(Fluoromethyl)cyclopropyl]-3-methoxybenzene (2f)

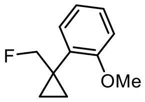


2f

The reaction was conducted with 57.9 mg (0.20 mmol) of **1f**. Product **2f** was purified by silica gel chromatography (silica gel, Et_2O/pentane, 0:100–4:96), further purified by PTLC, and obtained in 69% yield (25.3 mg, 0.14 mmol, colorless oil) with small amounts of phenylboronic acid pinacol ester.

^{1}H NMR (392 MHz, $CDCl_3$ (through Al_2O_3)): δ 0.91–1.04 (m, 4H), 3.81 (s, 3H), 4.43 (d, *J* = 48.6 Hz, 2H), 6.75–6.81 (m, 2H), 6.94 (dd, *J* = 0.78, 7.4 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7 (*C*H_2), 11.8 (*C*H_2), 25.9 (d, *J* = 23.0 Hz, *C*), 55.1 (*C*H_3), 90.5 (d, *J* = 172.5 Hz, *C*H_2), 111.9 (*C*H), 114.4 (*C*H), 120.8 (*C*H), 129.3 (*C*H), 143.6 (*C*), 159.5 (*C*). ^{19}F NMR (373 MHz, $CDCl_3$): δ –211.4 – –210.4 (m, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{11}H_{13}FO$, 180.0950; found, 180.0949.

1-[1-(Fluoromethyl)cyclopropyl]-2-methoxybenzene (2g)

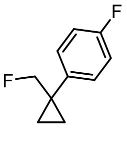


2g

The reaction was conducted with 57.5 mg (0.20 mmol) of **1g**. Product **2g** was purified by silica gel chromatography (silica gel, Et_2O/pentane, 0:100–4:96), further purified by PTLC, and obtained in 29% yield (10.6 mg, 0.058 mmol, colorless oil).

^{1}H NMR (401 MHz, $CDCl_3$ (through Al_2O_3)): δ 0.80–0.96 (m, 4H), 3.85 (s, 3H), 4.41 (d, *J* = 49.3 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.90 (td, *J* = 0.50, 7.4 Hz, 1H), 7.25 (td, *J* = 1.3, 7.5 Hz, 1H), 7.30 (dd, *J* = 2.0, 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.39 (*C*H_2), 10.44 (*C*H_2), 23.1 (d, *J* = 23.9 Hz, *C*), 55.2 (*C*H_3), 89.7 (d, *J* = 169.6 Hz, *C*H_2), 110.3 (*C*H), 120.2 (*C*H), 128.3 (*C*H), 129.2 (*C*), 131.9 (*C*H), 158.8 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –213.2 – –212.3 (m, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{11}H_{13}FO$, 180.0950; found, 180.0945.

1-Fluoro-4-[1-(fluoromethyl)cyclopropyl]benzene (2h)

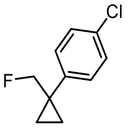


2h

The reaction was conducted with 110.4 mg (0.40 mmol) of **1h**. Product **2h** was purified by silica gel chromatography (silica gel, Et_2O/pentane, 0:100–2:98), further purified by GPC, and obtained in 21% yield (14.1 mg, 0.084 mmol, highly volatile colorless oil).

^{1}H NMR (392 MHz, $CDCl_3$): δ 0.95 (s, 4H), 4.38 (d, *J* = 49.4 Hz, 2H), 4.45 (s, 1H), 6.95–7.04 (m, 2H), 7.28–7.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.41 (*C*H_2), 11.47 (*C*H_2), 25.4 (d, *J* = 23.0 Hz, *C*), 90.6 (d, *J* = 172.4 Hz, *C*H_2), 115.1 (d, *J* = 21.1 Hz, *C*H), 130.4 (d, *J* = 7.7 Hz, *C*H), 137.6 (d, *J* = 3.9 Hz, *C*), 161.7 (d, *J* = 246.2 Hz, *C*). ^{19}F NMR (367 MHz, $CDCl_3$): δ –211.8– –210.8 (m, 1F), –116.6 (s, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{10}H_{10}F_2$, 168.0751; found, 168.0747.

1-Chloro-4-[1-(fluoromethyl)cyclopropyl]benzene (2i)

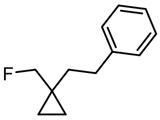


2i

The reaction was conducted with 117.0 mg (0.4 mmol) of **1i**. Product **2i** was purified by silica gel chromatography (silica gel, Et_2O/pentane, 0:100–2:98), further purified by GPC, and obtained in 22% yield (16.5 mg, 0.089 mmol, colorless oil).

^{1}H NMR (396 MHz, $CDCl_3$): δ 0.93–1.01 (m, 4H), 4.40 (d, *J* = 48.7 Hz, 2H), 7.30–7.72 (m, 4H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.67 (*C*H_2), 11.73 (*C*H_2), 25.4 (d, *J* = 23.9 Hz, *C*), 90.3 (d, *J* = 172.4 Hz, *C*H_2), 128.4 (*C*H), 130.0 (*C*H), 132.5 (*C*), 140.4 (*C*). ^{19}F NMR (373 MHz, $CDCl_3$): δ –211.5– –210.7 (m, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{10}H_{10}ClF$, 184.0455; found, 184.0453.

{2-[1-(Fluoromethyl)cyclopropyl]ethyl}benzene (2j)

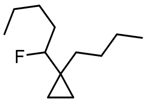


2j

The reaction was conducted with 114.4 mg (0.40 mmol) of **1j**. Product **2j** was purified by silica gel chromatography (silica gel, Et_2O/hexane, 0:100–4:96), further purified by GPC, and obtained in 42% yield (30.2 mg, 0.17 mmol, colorless oil).

^{1}H NMR (401 MHz, $CDCl_3$): δ 0.43–0.485 (m, 2H), 0.491–0.55 (m, 2H), 1.68–1.77 (m, 2H), 2.70–2.79 (m, 2H), 4.26 (d, *J* = 48.9 Hz, 2H), 7.14–7.23 (m, 3H), 7.26–7.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.16 (*C*H_2), 10.22 (*C*H_2), 20.6 (d, *J* = 23.0 Hz, *C*), 33.3 (*C*H_2), 36.6 (*C*H_2), 89.6 (d, *J* = 169.6 Hz, *C*H_2), 125.7 (*C*H), 128.3 (*C*H_2), 128.3 (*C*H_2), 142.3 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –213.2 – –212.3 (m, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{12}H_{15}F$, 178.1158; found, 178.1156.

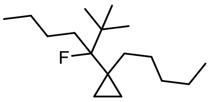
1-Butyl-1-(1-fluoropentyl)cyclopropane (2k)



2k

The reaction was conducted with 117.8 mg (0.40 mmol) of **1k**. Product **2k** obtained 53% ^{19}F NMR yield (Isolation was failed because of its instability). The same reaction was conducted with 118.0 mg (0.40 mmol) of **1k**. Product **2k** was obtained 72% ^{19}F NMR yield (Isolation was failed because of its instability). HRMS–EI (m/z): $[M]^+$ calcd for $C_{12}H_{23}F$, 186.1784; found, 186.1781.

1-(3-Fluoro-2,2-dimethylheptan-3-yl)-1-pentylcyclopropane (2l)

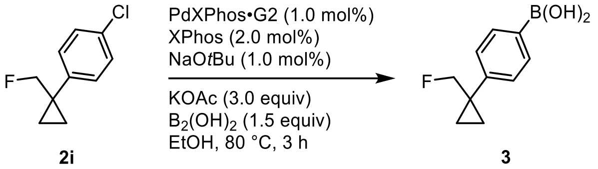


2l

The reaction was conducted with 72.6 mg (0.20 mmol) of **1l**. Product **2l** was purified by silica gel chromatography (silica gel, Et_2O/hexane, 0:100–1:99) obtained in 73% yield (37.3 mg, 0.15 mmol, colorless oil).

^{1}H NMR (396 MHz, $CDCl_3$): δ 0.22–0.34 (m, 2H), 0.65–0.81 (m, 2H), 0.82–1.0 (m, 7H), 1.05 (s, 9H), 1.07–1.53 (m, 10H), 1.59–1.73 (m, 1H), 1.74–1.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.7 Hz, CH_2), 8.06 (d, *J* = 5.8 Hz, CH_2), 14.1 (CH_3), 14.2 (CH_3), 22.6 (*C*), 22.7 (d, *J* = 23.8 Hz, *C*), 23.6 (CH_2), 25.4 (CH_2), 26.4 (d, *J* = 3.9 Hz, CH_2), 27.6 (d, *J* = 10.0 Hz, CH_2), 32.5 (CH_2), 33.2 (d, *J* = 6.7 Hz, CH_2), 33.3 (d, *J* = 23 Hz, CH_2), 40.4 (d, *J* = 22.9 Hz, CH_2), 100.1 (d, *J* = 82.1 Hz, *C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –171.7 (d, *J* = 69.3 Hz, 1F). HRMS–EI (m/z): $[M]^+$ calcd for $C_{17}H_{33}F$, 256.2566; found, 256.2565.

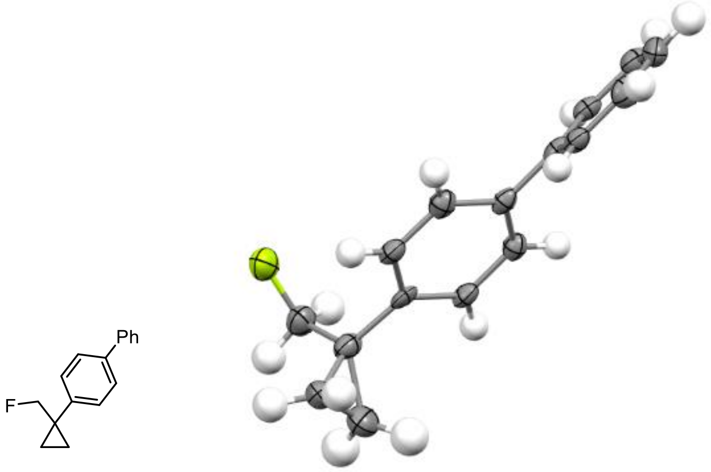
3.10. Synthetic Application of Products[17]



Cross-coupling of **2i** was performed according to the literature procedure.**[17]** In an oven-dried reaction, the vial transferred to an argon-filled glove box. PdXPhos·G2 (1.9 mg, 0.00246 mmol), NaO*t*Bu (0.4 mg, 0.00492 mmol), KOAc (72.2 mg, 0.738 mmol), $B_2(OH)_4$ (33.2 mg, 0.370 mmol) and XPhos (2.6 mg, 0.00495 mmol) were placed in the reaction vial, and then the vial was capped with a rubber septum and removed from the glovebox. The vial with reagents was suspended in EtOH (740 μL). After that, **2i** (45.4 mg, 0.246 mmol) was added to the mixture; then the mixture was allowed to stir at 80 ºC for 3 h. After completing the reaction, the mixture was passed through a short plug of silica gel (Φ: 10 mm, the height of the silica-gel column: 30 mm), eluted with acetone, and the volatiles were removed in vacuo. The resultant mixture was purified again by silica gel chromatography (Et_2O/hexane, 5:95–10:90, Acetone) to give **3** (35.2 mg, 0.18 mmol, 74%) as pale ivory solid. ^1H NMR (401 MHz, $CDCl_3$): δ 0.99–1.13 (m, 4H), 4.52 (d, *J* = 48.5 Hz, 2H), 7.46–7.48 (m, 2H), 8.16–8.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 12.39 (CH_2), 12.45 (CH_2), 25.8 (d, *J* = 22.0 Hz, *C*), 90.2 (d, *J* = 171.2 Hz, CH_2), 127.7 (*C*H), 135.7 (*C*H), 146.8 (*C*). ^{19}F NMR (377 MHz, $CDCl_3$): δ –211.4 – –210.7 (m, 1F). HRMS–ESI (m/z): $[M–H]^+$ calcd for $C_{10}H_{11}O_2BF$, 192.0878; found, 192.0878.

3.11. Single Crystal X-ray Structural Analysis

The stereochemistry of **2b** was determined by X-ray crystallographic analysis. The details are summarized in Figure 1 and Table 1.



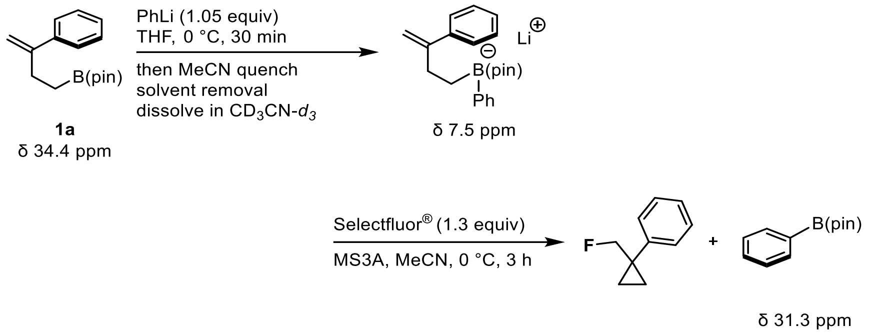
2b

Figure 1. Molecular structure of **2b**

Table 1. Summary of X-ray crystallographic data for **2b**.

CCDC number	2261296
Empirical Formula	$C_{16}H_{15}F$
Formula Weight	226.28
Crystal System	Monoclinic
Crystal Size	0.3×0.2×0.03
a / *Å*	28.1132(9)
b / *Å*	5.7439(2)
c / *Å*	14.9497(4)
α / ^{o}	90
β / ^{o}	98.636(3)
γ / ^{o}	90
V / $Å^3$	2386.70(13)
Space Group	$P2_1$
Z value	8
*D*calc / g cm^{-3}	1.259
Temperature / K	123
No. of Reflections	Total: 12107
Measured	7153 (R_{int} = 0.0226)
Residuals: R_1 (I > 2.00σ (*I*)) / %	0.0643
Residuals: wR_2 (All reflections) / %	0.3579
Goodness of Fit (GOF)	1.258
Maximum peak in Final Diff. Map / $Å^3$	0.29 e^-
Minimum peak in Final Diff. Map / $Å^3$	–0.33 e^-
Flack parameter	0.4(2)

3.12. Details of ^{11}B NMR Experiments



Homoallylic boronate **1a** (51.8 mg, 0.2 mmol) was placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a Teflon®-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (2 mL) was added to the vial through the rubber septum using a syringe and allowed to cool to 0 °C and stirred for 10 min. After stirring for 10 min, phenyl lithium (115 µL, 1.05 equiv) was added to the mixture. The reaction mixture was stirred at 0 °C for 30 min. After stirring for 30 min, the mixture was stirred at room temperature for 10 min. After stirring for 10 min at room temperature, the solvent (THF) was then removed in vacuo and the crude dissolved in CD_3CN-d_3 (1.4 mL). The resulting mixture was transferred to an NMR tube under the N_2 atmosphere and analyzed by $^{11}B\{^{1}H\}$ NMR spectroscopy (JEOL JNM-ECA400) at room temperature.

The solution in the NMR tube was transferred to the rest of the boronate complex solution in a vial tube with CD_3CN-d_3 (0.6 mL) and allowed to cool to 0 °C and stirred for 10 min (The boronate complex solution is total 2 ml in CD_3CN-d_3). Another oven-dried reaction vial was charged with MS 3A (80 mg) and dried up with a heat gun in vacuo. After Selectfluor® (92.1 mg, 1.3 equiv) was placed, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. CD_3CN-d_3 (1.4 mL) was added and allowed to cool to 0 °C, stirred 10 min at the same temperature. The boronate complex solution (2.0 mL in CD_3CN-d_3) was added to the vial containing Selecfluor® solution dropwise at 0 °C with CD_3CN-d_3 (0.6 mL) and stirred at 0 °C for 3 h. After being stirred for 3 h, the resulting mixture was transferred to an NMR tube under the N_2 atmosphere and analyzed by $^{11}B\{^{1}H\}$ NMR spectroscopy (JEOL JNM-ECA400) at room temperature.

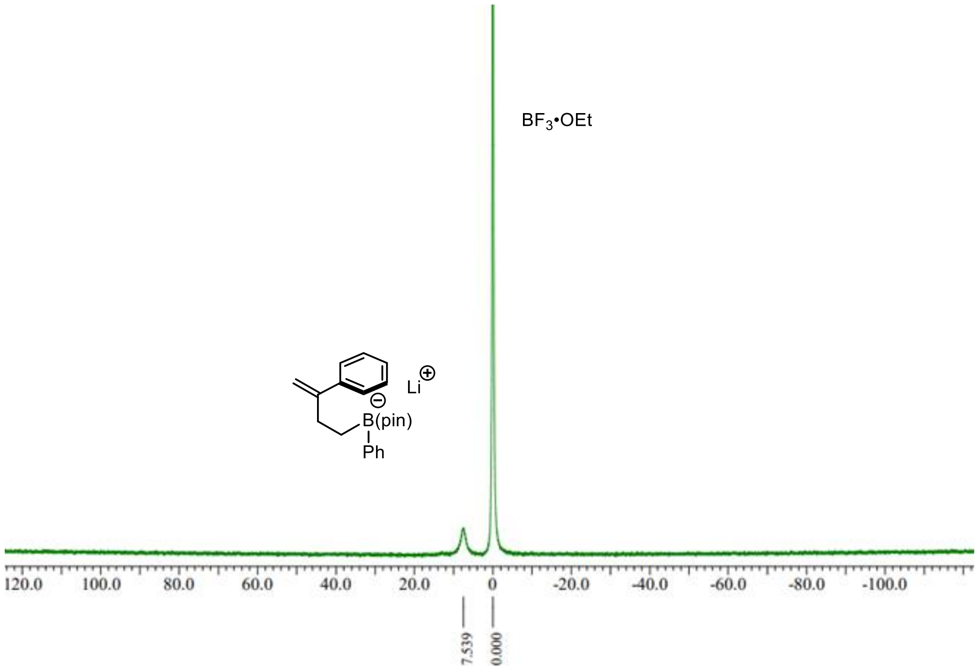


Figure 2. $^{11}B\{^1H\}$ NMR spectra of boronate complex at room temperature

3.13. References

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IV Summary of This Thesis

Organofluorine compounds have been recognized as the important molecules in organic chemistry especially material chemistry and medicinal chemistry. Following the attention, approaches to construction of organofluorine compounds have been in constant evolution. Organoboron compounds are valuable synthetic intermediates in organic synthesis for the construction of complex molecules and functional materials, such as novel fluorescent materials, electron transport materials, and pharmaceuticals. In this thesis, I focused on the development of novel organofluorine compounds using organoboron compounds as intermediates.

In Chapter 2, I developed the enantioselective γ-boryl substitution of trifluoromethyl- and silyl-substituted alkenes using a copper(I)/diboron catalyst system. This is the first report to construct *gem*-difluoro allylboronates, which have quaternary stereogenic carbon centers with boron moiety and silicon moiety on the same carbon. This reaction was achieved by using an optically active C_1 symmetric QuinoxP*-type bisphosphine ligand that was developed in the Ito laboratory. The products were obtained in high yield with high enantioselectivity. Furthermore, the products were converted into a variety of fluorinated compounds via oxidation, allylboration reaction, and cross-coupling reaction. The author estimated that the trifluoromethyl group, in which one of the fluorine atoms acts as a leaving group, is located at the sterically less hindered region of the ligand to avoid any steric repulsion between the ligand and substrate in the enantio-determining transition state. That is the key to obtain the desired enantiomer.

In Chapter 3, I developed the electrophilic cyclization via the boronate complex between various homoallylic boronates and Selectfluor® use of phenyl lithium. This reaction provides a fluoromethylated cyclopropane ring that was difficult to synthesize by conventional methods. In this reaction, a variety of substrates can be applied. Furthermore, the intermediate boronate complex was observed by ^{11}B NMR experiments. The fluoromethylated cyclopropane was successfully applied to synthesize a building block bearing fluoromethyl-substituted cyclopropane for a bioactive compound.

Through this thesis, I developed to synthesize novel organofluorine compounds, which have never been synthesized before the use of organoboron compounds. As the author demonstrated, each product could be used as new fluorine-containing building blocks in organic synthesis. These reactions would be one of the valuable methods to synthesize new organofluorine compounds in material and pharmaceutical chemistry.

V List of publication

Chapter II:

Cu(I)-Catalyzed Enantioselective γ-Boryl Substitution of Trifluoromethyl- and Silyl-substituted Alkenes

Oyama, N.; Akiyama, S.; Kubota, K.; Imamoto, T.; Ito, H. *Eur. J. Org. Chem,* **2022**, e202200664.

Chapter III:

Synthesis of Fluoromethyl-substituted Cyclopropanes by Electrophilic Cyclization of Homoallylic Boronate Intermediates

Oyama, N.; Ito, H. *Adv. Synth. Catal.* **2023**, *accepted.* DOI:10.1002/adsc.202300529

Other publications

Copper(I)-Catalyzed Radical Relay Reaction Enabling the Intermolecular 1,2-Alkylborylation of Unactivated Olefins

Akiyama, S.; Oyama, N.; Endo, T.; Kubota, K.; Ito, H. *Eur. J. Am. Chem. Soc.,* **2021**, *143*, 5260.

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2023